The British Journal of Surgery

Volume 74, Number 1, January 1987

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PIPRIL

INTRAMUSCULAR/INTRAVENOUS PIPERACILLIN

Still a key move
in surgical infections

- Proven single agent activity[1-3]
- Broad spectrum cover, including anaerobes.[4] Active against *Strep. faecalis*[5] – unlike cephalosporins, aminoglycosides and metronidazole.
- Highly synergistic with aminoglycosides[6,7]
- Low potential for inducible resistance compared with 'third generation' cephalosporins[8,12]
- Effective concentrations in bile and peritoneal fluid[9,10]
- Well tolerated[11]

Prescribing Information. **Indications:** Pipril is a broad spectrum bactericidal penicillin for the treatment and peri-operative prophylaxis of systemic or local infections caused by sensitive organisms. **Dosage:** Adult patients with normal renal function should receive 4-8g daily in divided doses for mild or uncomplicated infections. In serious or life-threatening infections 12-16g daily in divided doses. For peri-operative prophylaxis 2g just prior to surgery followed by at least two doses of 2g at four or six hour intervals. Patients with renal insufficiency may need dosage reduction – see Data Sheet. Children 2 months to 12 years of age: 100-300 mg/kg daily in three to four divided doses. Neonates and infants under two months of age: 100-300 mg/kg daily in two equally divided doses. **Contra-indications:** Penicillin or severe cephalosporin hypersensitivity. **Precautions:** Safety for use in pregnant or lactating women has not yet been established. **Side effects:** Uncommon and typical of injectable penicillins. **Administration:** Pipril is presented as 1g or 2g vials, 4g infusion bottles and 4g infusion packs containing piperacillin as piperacillin sodium. See Data Sheet or package leaflet for full details of preparation and administration. **Product Licence No.** 0095/0073. **Basic NHS Price:** 1g vial £2.98. 2g vial £5.90. 4g infusion bottle £11.66. 4g infusion pack (4g bottle, 50 ml WFI plus needle) £12.43. Further information is available on request.

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Prescribing information

Dosage Adults: Generally 750mg t.i.d. i.m. or i.v. Severe infections 1·5 grams t.i.d. i.v. Frequency of injections can be increased to six-hourly if necessary. Infants and children: 30 to 100mg/kg/day in three or four divided doses. 60mg/kg/day will be appropriate for most infections. Neonates: 30 to 100mg/kg/day in two or three divided doses. Gonorrhoea: Single dose of 1·5 grams (2 x 750mg into different sites). Prophylaxis: The usual dose of 1·5 grams i.v. with induction of anaesthesia for abdominal, pelvic and orthopaedic operations, may be supplemented with two 750mg i.m. doses eight and sixteen hours later. In cardiac, pulmonary, oesophageal and vascular operations, the usual dose is 1·5 grams i.v. with induction of anaesthesia continuing with 750mg i.m. t.i.d. for a further 24 to 48 hours. In total joint replacement, 1·5 grams cefuroxime powder may be mixed dry with each pack of methyl methacrylate cement monomer before adding the liquid polymer.

Contra indications Hypersensitivity to cephalosporins.

Precautions Cephalosporins may, in general, be given safely to patients who are hypersensitive to penicillins. Care is indicated in patients who have experienced an anaphylactic reaction to penicillin. As with all drugs, Zinacef should be administered with caution during the early months of pregnancy. Zinacef does not interfere with enzyme-based tests for glycosuria. Slight interference with copper reduction methods may be observed. Zinacef may cause false-negative results in the ferricyanide test for glucose. This antibiotic does not interfere in the alkaline picrate assay for creatinine. Zinacef should not be mixed in the syringe with aminoglycoside antibiotics. Reduce dosage when renal function is markedly impaired. Cephalosporins at high dosage should be given with caution to patients receiving concurrent treatment with potent diuretics such as frusemide, as these combinations are suspected of adversely affecting renal function. Clinical experience with Zinacef has shown that this is not likely to be a problem at the recommended dose levels.

Side effects Adverse reactions are rare and generally mild and transient, e.g., rashes, gastro-intestinal disturbances, decreased haemoglobin concentration, eosinophilia, a positive Coombs' test, transient rises in serum liver enzymes and transient pain (after i.m. injection). As with other antibiotics, prolonged use may result in the overgrowth of non-susceptible organisms, e.g. Candida.

Product Licence Number: 4/0263

Recommended price (exclusive of VAT): 5 x 250mg £4·41; 5 x 750mg £13·19; 1·5 gram £5·29; 1·5 gram infusion pack £5·29. Further information on Zinacef (trade mark) is available from:

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Cover picture

The Association of Surgeons of Great Britain and Ireland
The cover shows the Presidential badge of the Association.

President: Professor R. Shields MD, FRCs(Ed), FRCS
Honorary secretary: Mr B. T. Jackson MS, FRCS

The Association office is situated at the Royal College of Surgeons of England, 35/43 Lincoln's Inn Fields, London WC2A 3PN, telephone number 01-405 6753.

Announcement

The Journal and the Surgical Research Society

As readers who glance at the banner of the Journal this month will see, we now have a formal link with the Surgical Research Society. This body was found in 1954 to promote surgical research of all kinds in Great Britain and Ireland and for many years the Journal has carried the abstracts of its meetings. We welcome the Society whose readers will now automatically receive the Journal as a consequence of their membership. The association of the premier body for surgical research in our islands with the Journal compliments and extends the longstanding relationship that we have had with the Association of Surgeons of Great Britain and Ireland which represents all that is best in clinical surgery.

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Dosage *Adults:* Generally 750mg t.i.d. i.m. or i.v. Severe infections 1·5g t.i.d. i.v. Frequency of injections can be increased to 6-hourly if necessary. *Infants and children:* 30 to 100mg/kg/day in 3 or 4 divided doses. 60mg/kg/day will be appropriate for most infections. *Neonates:* 30 to 100mg/kg/day in 2 or 3 divided doses. *Gonorrhoea:* Single dose of 1·5g (2 x 750mg into different sites). *Prophylaxis:* The usual dose of 1·5g i.v. with induction of anaesthesia for abdominal, pelvic and orthopaedic operations, may be supplemented with two 750mg i.m. doses 8 and 16 hours later. In cardiac, pulmonary, oesophageal and vascular operations, the usual dose is 1·5g i.v. with induction of anaesthesia continuing with 750mg i.m. t.i.d. for a further 24 to 48 hours. In total joint replacement, 1·5g cefuroxime powder may be mixed dry with each pack of methyl methacrylate cement polymer before adding the liquid monomer.
Contra-indication Hypersensitivity to cephalosporins.
Precautions Cephalosporins may, in general, be given safely to patients who are hypersensitive to penicillins. Care is indicated in patients who have experienced an anaphylactic reaction to penicillin. As with all drugs, Zinacef should be administered with caution during the early months of pregnancy. Zinacef should not be mixed in the syringe with aminoglycoside antibiotics. Reduce dosage when renal function is markedly impaired. (See Data Sheet for details). Cephalosporins at high dosage should be given with caution to patients receiving concurrent treatment with potent diuretics such as frusemide, as these combinations are suspected of adversely affecting renal function. Clinical experience with Zinacef has shown that this is not likely to be a problem at the recommended dose levels.
Side effects Adverse reactions are rare and generally mild and transient, e.g., hypersensitivity reactions (rashes and rarely anaphylaxis), gastro-intestinal disturbances, decreased haemoglobin concentration, eosinophilia, leucopenia, neutropenia and a positive Coombs' test. Transient rises in serum liver enzymes. Transient pain after i.m. injection. As with other antibiotics, prolonged use may result in the overgrowth of non-susceptible organisms, e.g., Candida.
Recommended price (exclusive of VAT): 5 x 250mg £4·41; 5 x 750mg £13·19; 1·5 gram £5·29; 1·5 gram infusion pack £5·29
Product licence number 0004/0263
Further information on Zinacef (trade mark) is available from:

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The Ulster Medical Society

The Ulster Medical Society was founded on 30 April 1862. It was formed by the amalgamation on that date of two previously existing societies: the Belfast Medical Society and the Belfast Clinical and Pathological Society.

The physicians and surgeons of Belfast, though only 19 in number, had formed the Belfast Medical Society in 1806 for mutual improvement in their common profession. Indeed, in its early days, the Society admitted apothecaries and even some non-professional gentlemen who approved of the Society and its aims. The Belfast Clinical and Pathological Society seems to have been a rival organization set up in 1853 but within a decade both Societies met and amalgamated.

The Society still has a wide membership from all the spectrum of medicine and each discipline is enriched by the input of the others. Surgeons have played a prominent part in the Society and one of the earliest Presidents of the Society, William McCormac, subsequently became President of the Royal College of Surgeons of England. Two subsequent Presidents of the Society became Presidents of the Royal College of Surgeons in Ireland, namely, Professor Andrew Fullerton and Sir Ian Fraser.

In this age of super-specialization and splinter groups it is a useful exercise for the hospital specialist, surgeon, physician, gynaecologist or whoever, to take time to get the broad view and a renewed sense of proportion as they meet with their general practitioner colleagues and others. Twice yearly the Society produces the *Ulster Medical Journal* which again reflects the wide interests of its members.

With regard to the Society crest, it should be pointed out that the left hand depicted in the centre is not the red hand of Ulster. The hand in the Ulster Medical Society crest is a left hand with some drops of blood below it whereas that of the Ulster arms is a right hand without any accompanying blood. Legend tells that as a marauding band of Vikings approached the coast of Northern Ireland in a longboat the leader said that the first man to touch land with hand or foot would be given the area. The sailors left their ship and entered a number of small boats and raced for the shore. A fierce sailor, with the most un-Viking name of O'Neill, realized that another small boat was winning the race. Quickly he drew his sword and with a single blow severed his left hand at the wrist. As they neared the shore he threw the now bloody left hand forward so that it touched land before any of his comrades. O'Neill was duly given the land and took the left hand for his crest. The snake is of course the symbol of Asclepius, the god of Medicine, son of Apollo and Coronis; he was taken from her womb shortly after her death. Coronis had been murdered by Artemis at the behest of a jealous Apollo. Asclepius was taught by Chiron the centaur and he grew up to be a skilled surgeon. It was said that he brought men and women from the very gates of the Underworld, restoring them to health when everyone had given them up for lost. Hades complained to Zeus that he was being robbed of his rightful subjects and, to appease the Lord of the Underworld, Zeus struck Asclepius dead. The crest uses two snakes rather than one merely for symmetry.

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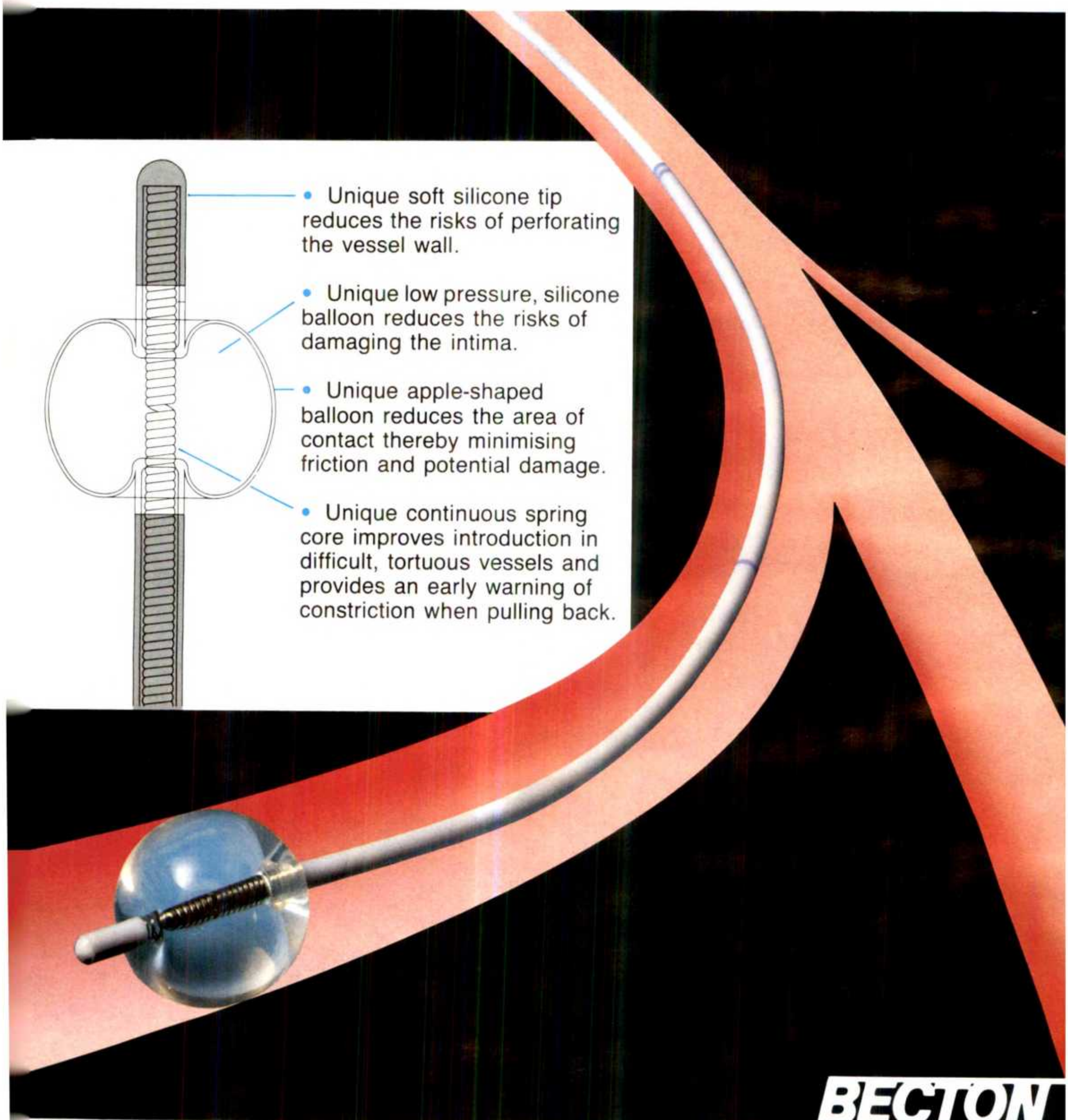

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Spontaneous regression of metastatic renal carcinoma

Cases of apparent regression of cancer excite the interest of doctors and the public at large, and have been cited as miracles in support of the cause of sanctification by the church[1].

Adenocarcinoma of the kidney is an interesting and unusual tumour: it can invade and extend along major veins[2] and produce tumour emboli; solitary giant ('cannon ball') metastases curable by surgical resection may occur[3]; its metastases can lie dormant for many years before becoming detectable[4] and it is responsible for a variety of non-metastatic syndromes[5]. To this catalogue can be added the fact that it is among the commonest of tumours which have been described as undergoing spontaneous regression[6]. In the current issue of this Journal (*Br J Surg* 1987; **74**: 69–70) there is recorded yet another such case: a patient who appeared to have pulmonary metastases from a large renal carcinoma in whom the radiological appearances of metastatic disease disappeared without treatment before the primary tumour was removed surgically.

The phenomenon of spontaneous regression of tumours raises a number of questions. Do the cases reported in the literature conclusively demonstrate that regression can occur? What is the mechanism for such regression? Could this mechanism be exploited in the treatment of cancer? What bearing does spontaneous regression have on the management of the condition and in particular should its possibility be borne in mind when treating a patient with an advanced renal tumour?

Predominately it is lung metastases which are said to regress[7] but unfortunately in many cases, as in the patient reported in this Journal, the presence of these metastases is based purely on radiological findings without confirmatory tissue diagnosis. The appearance of pulmonary metastases is characteristic and such an appearance in a patient known to have a malignant tumour is rightly considered to be diagnostic. However other pulmonary conditions can mimic this appearance and it is possible that some cases of apparent tumour regression are due to a coincidental inflammatory condition affecting the lungs. The non-metastatic effects which are a not infrequent feature of localized renal carcinoma could perhaps make patients more susceptible to such conditions. However, of the 51 patients discussed by Freed and his colleagues[7], 19 had histological confirmation of metastatic disease and the phenomenon of regression is difficult to dispute.

Although hormonal effects, fever, infection and other agencies have been put forward, the most popular explanation for idiopathic regression is that it is a manifestation of some immunological process[7]. Immunological suppression of renal tumour metastases might account for the long latent period sometimes seen before their clinical appearance, and it is postulated that the adverse effect on survival of blood transfusion described in colonic carcinoma[8] might also apply to patients with renal carcinoma[9]. The situation more usual than that described in this Journal, namely regression following nephrectomy[10], has been explained on the basis of stimulation of the immune system by surgery. In view of the disappointing results of chemotherapy for renal tumours, immunological treatment has been explored but reports of its use are sporadic and somewhat anecdotal[11], and the effects of Interferon in the management of metastatic renal cancer have yet to be proved[12]. The possibility that pre-operative tumour infarction by embolization might produce beneficial immunological effects recently excited interest but the initial report from the M. D. Anderson Institute suggesting improved survival[13] has not been confirmed.

Although the dramatic occurrence of complete spontaneous regression is rare[14], spontaneous fluctuation in the size of metastases may be more common. Those studying new treatments for metastatic renal carcinoma are well advised to remember this when considering response rates. Of more relevance to most urologists is whether a patient with metastatic renal carcinoma should undergo nephrectomy in the hope that this might be followed by regression. Given the rarity of complete regression, it would be unjustifiably optimistic to advise nephrectomy merely for this reason. However, nephrectomy is an effective way of controlling a primary tumour which, even if asymptomatic at diagnosis, might later cause troublesome haematuria or pain. Given

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that many patients with advanced disease may die before this occurs[15], embolization or ablation by intra-arterial injection of ethanol[16] might be considered useful alternatives. If the tumour bulk of the primary is greater than that of the metastases, removal of the kidney may temporarily improve the patient's health, particularly if the renal tumour has been exerting a significant non-metastatic effect. The patient's mental well-being may also be improved by nephrectomy if he is aware of the diagnosis. Like most difficult clinical decisions no general guidelines can really be given; the situation needs careful consideration for each individual. However, spontaneous regression is so rare a bonus that it is not a significant incentive to operate[6].

What is clear about renal carcinoma is the unpredictability of its behaviour. The author has a patient under his care who is alive and well over two and a half years after the diagnosis of pulmonary metastases from a renal tumour removed six months earlier. Prolonged survival can also occur in patients in whom the primary tumour is not removed. Idiopathic regression perhaps represents one further stage towards this end of the spectrum, a spectrum which unfortunately has at its other end the patient who dies within months of the removal of an apparently localized tumour.

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Orthotopic liver transplantation: postoperative complications and their management

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The Birmingham liver transplant programme started in 1982. Forty-six patients have been transplanted with a follow-up of 3 months or longer. Twenty-seven patients are still alive, of whom sixteen have lived for more than one year. The 30 day hospital mortality was 30·4 per cent and the actuarial predicted one year survival 55·5 per cent. Four patients have been regrafted for chronic rejection and graft failure. Thirteen patients have required surgery in the postoperative period for: bleeding (two), removal of abdominal packs (four), biliary leaks and obstruction (five), duodenal perforation (one) and small bowel obstruction (one). Acute rejection was common, occurring in 30 patients and progressing to chronic rejection in 4. Ten patients developed renal failure with an 80 per cent mortality and eleven patients developed grand mal fits. Severe bleeding (> 70 units) was associated with previous abdominal surgery and a high mortality (88·9 per cent). Opportunistic fungal infection carried a 100 per cent mortality. Although more than half of all transplanted patients will survive for more than one year, the postoperative period is still one of high morbidity and mortality.

Keywords: Liver transplantation, cyclosporin A, postoperative complications

The first human orthotopic liver transplants were performed in the 1960s by Starzl[1] and Calne[2]. Initially, only patients with terminal liver disease were considered for transplantation and few patients survived the complex surgical procedure and postoperative period[3]. In the 20 years that followed the first attempt at liver transplantation, results remained poor with only a quarter of adult patients surviving 12 months[4]. However, with growing experience and greater understanding of many of the technical and immunological aspects[5], patients began to be referred before the final phase of their liver disease, thus affording a more realistic prospect of survival. Patients transplanted for primary hepatocellular carcinoma had less operative mortality but tended to die subsequently from recurrent disease[6]. In adult cirrhotics a high proportion of deaths in the early postoperative period followed either technical complications and bleeding[4], or overwhelming sepsis associated with high steroid administration[7] and biliary complications[8]. At the National Institute of Health Consensus Conference[9] the four major centres reported their experience of liver transplantation confirming the continuing high incidence of postoperative deaths. They reported perioperative mortality rates (within 48 h of transplantation) of 5–15 per cent of patients with a further 12–20 per cent of patients dying within the first 30 days postoperatively[10].

Since the early 1980s, however, a steady improvement in results of liver transplantation has been reported from experienced centres[11]. This improvement has been attributed to a number of possible factors: a more realistic evaluation and referral pattern of patients with liver disease[12], an improvement in operative techniques including the use of venovenous bypass[13,14], and improvements in biliary reconstruction[15,16] with a reduction in biliary obstruction and sludging[17]. These developments have, however, usually been combined with the introduction of the non-steroidal immunosuppressive agent cyclosporin A which has allowed significant reduction in the administration of steroids in the early postoperative period[18]. In addition to these technical and immunological improvements there has been a growing realization that re-transplantation of patients with primary technical failures or hepatic rejection is feasible, thus further reducing the numbers of patients dying following transplantation[19]. The absence of any controlled trials in liver replacement makes it difficult to evaluate the relative importance of these individual factors. Nevertheless, improved results with over 70 per cent of children surviving at one year after transplantation and over 60 per cent of adults in the Pittsburgh series being alive and well at one year[18] have encouraged a number of other units to initiate liver replacement programmes. It is estimated that there are now over 20 centres within Europe alone planning to initiate liver replacement programmes.

While much of the improvement in results may be attributed to the factors listed above, a growing familiarity with the management of these difficult patients in the critical postoperative period has undoubtedly played a major role in experienced centres.

Despite more experience in dealing with patients during this complex phase significant clinical problems are still encountered, and as new centres begin liver transplantation programmes it seemed timely to review the current postoperative problems encountered following orthotopic transplantation in patients receiving cyclosporin A and low dose steroids. The majority of earlier reports of postoperative care have been in the pre-cyclosporin era and have highlighted the high incidence of steroid related deaths from infection, biliary complications, and bleeding peptic ulcers[4]. The purpose of this paper is to review the experience of one recently established liver transplant centre and to examine the major postoperative problems encountered, using current surgical techniques and immunosuppressive protocols, after the first 50 transplants.

The frequency and nature of complications following major surgery also reflects patient selection and operative management and these aspects will also briefly be outlined.

Patients and methods

The liver transplantation programme at the Queen Elizabeth Hospital began in January 1982 and in that year three patients underwent liver replacement. In 1983 there were six transplants. In 1984, 7 patients were transplanted and in 1985 17 patients underwent liver transplantation. There have been 13 further patients transplanted up to May 1986. In all,

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therefore, 46 patients underwent liver transplantation in the initial 4 year period (*Figure 1*). Four of these required re-grafting, making a total of fifty liver transplant operations. All have now been followed up for a minimum of 3 months. The initial indications for consideration of liver transplantation were patients with either chronic liver disease with a life expectation of less than 6 months and associated major disability, or otherwise unresectable primary liver cancer (*Figure 2*). Patients' ages have ranged from 11 to 60 (mean 34). Children under the age of 10 were not considered for surgery in the early phase of the programme. Thirteen patients have been transplanted for primary hepatic malignancies. Seven patients had multicentric primary hepatocellular carcinomas, restricted to the liver, three of which were fibrolamellar variants. Three patients had hepatoma within a cirrhotic liver. There were two patients with intrahepatic cholangiocarcinoma and one patient with an epithelioid haemangio-endothelioma[20]. Their ages ranged from 13 to 60 (mean 41).

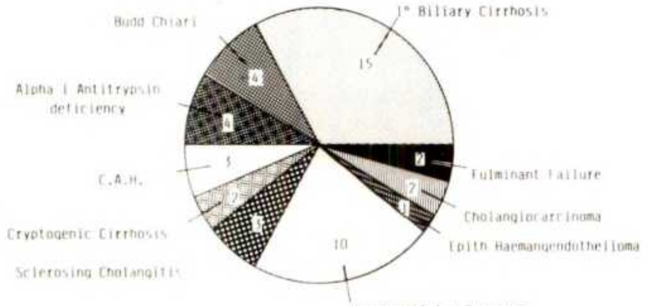

Figure 1 *This pie chart shows the diseases encountered in the 46 patients receiving 50 transplanted livers in the initial phase of the liver transplant programme. CAH, chronic active hepatitis*

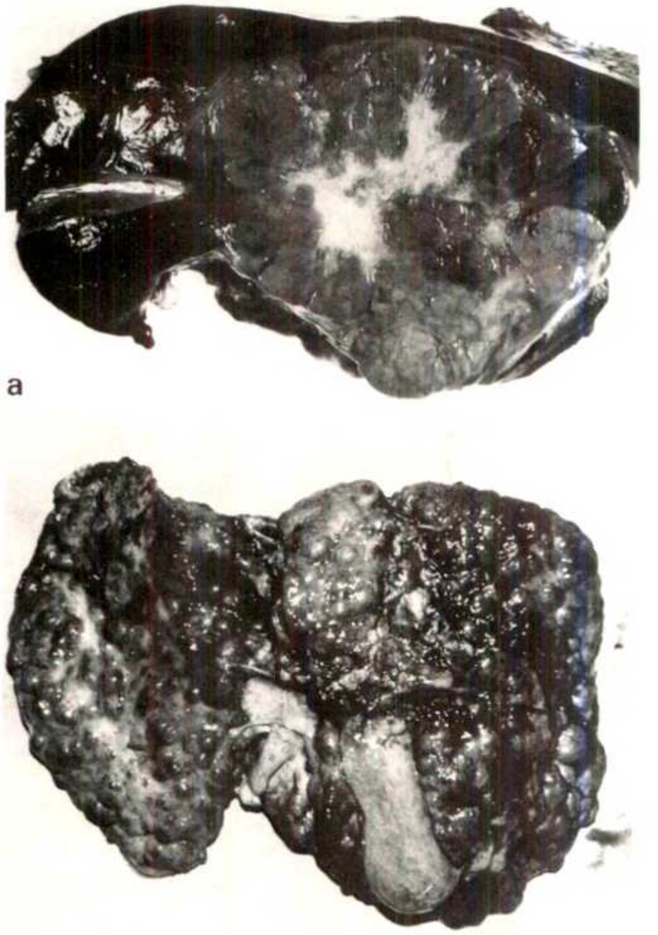

Figure 2 *Two excised livers, showing multicentric tumour* (**a**) *and ena stage cirrhosis* (**b**)

This latter group form a small proportion of patients referred with apparent primary hepatocellular carcinoma for consideration of transplantation. Of the 36 patients reviewed during this time who were thought to have primary hepatocellular carcinoma, 9 proved to have secondary hepatic malignancy, 1 a benign hepatic cyst, and 1 an acute Budd–Chiari syndrome. Major hepatic resection proved feasible in three other patients, obviating the need for hepatic transplantation and disease extended beyond the liver in the remaining patient, thereby excluding surgical treatment. Patients with advanced hepatic cirrhosis underwent detailed joint medical and surgical review before admission to the programme. Sixty-one per cent of the cirrhotic patients had been in-patients at the time of transplantation or had required intensive therapy care for prolonged periods because of advanced hepatic disease with hepatic failure, encephalopathy or renal failure, and were thus considered relatively high risks for transplantation. Six patients died from complications of chronic liver disease during this period (variceal bleeding and renal failure) whilst on the active transplant list, waiting for a suitable donor.

Operative management

Before surgery patients received chest physiotherapy and were given prophylactic anti-fungal agents and antibiotics, (amphotericin lozenges orally, nystatin 200 000 units orally and cefotaxime 2 g intravenously). These were continued postoperatively.

The liver was always harvested with the kidneys and in conjunction with the heart or heart/lung on 12 occasions. In the first 24 donors 4°C Collin's solution (South Glamorgan H. A. Pharmaceutical Services) was used for perfusion of the liver, while the kidneys were separately perfused with 4°C hypertonic citrate (Marshall's solution, Travenol Laboratories). In the last 26 liver harvestings hypertonic citrate solution was used for *in situ* perfusion of both the kidneys and the liver by total abdominal organ perfusion.

The recipient operation was performed in a standard fashion[21]. Unlike some centres, hepatic venovenous bypass[13,14] has not been used to support the systemic circulation or decompress the portal circulation. Two patients developed ventricular fibrillation at the time of removal of the upper caval cross clamp and required cardioversion. Air embolism is also a hazard at this time[22], and a small air bolus occurred in two patients (OL20 and OL31) as noted by changes in CO_2 monitoring. This was not, however, of clinical significance.

A gallbladder conduit was fashioned for all but one patient (*Figure 3*)[15]. Five patients (OL13, OL24, OL29, OL31 and OL44) had a Roux-en-Y cholecystojejunostomy performed because of a small recipient common bile duct or sclerosing cholangitis. One patient (OL21) had a direct end-to-end choledochocholedochostomy performed because the donor had had a cholecystectomy.

Haemostasis at the time of transplantation could not be achieved in five patients (OL1, 11, 13, 20, 28 and 44) because bleeding from the under

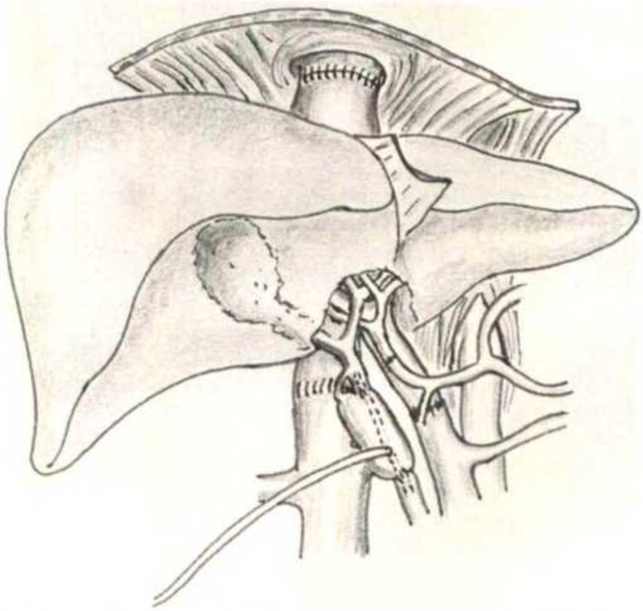

Figure 3 *Surgical anatomy of liver transplantation. This diagram shows the two caval anastomoses, the portal vein and hepatic artery anastomoses together with the gallbladder conduit (see text). Modified from* Figure 4 *in Jenkins RL, Benotti PN, Bothe AA* et al. *Liver transplantation.* Surg Clin N Am *1985;* **65:** *103–22, with permission*

surface of the diaphragm and right adrenal area could not be controlled, in spite of extended efforts, by standard methods and intra-abdominal packing was needed. Four of these patients had portal hypertension associated with dense adhesions, three from previous surgery and one from a haemoperitoneum following an open liver biopsy. The other (OL28) had had two previous exploratory and investigative laparotomies for a hepatocellular carcinoma.

Operative anaesthetic management

The major problems during anaesthesia for orthotopic liver transplantation are those of haemodynamic changes associated with bleeding, cross-clamping of the inferior cava and biochemical derangement[21]. In the last 24 cases use of the Haemonetic cell saver (Haemonetic Corp., Braintree, Boston, MA, USA) allowed the majority of blood spilt during the recipient liver dissection to be removed from the operative field by suction and the red cells separated out by the cell saver for re-transfusion in normal saline, accompanied by the transfusion of clotting factors and platelets. This not only produced a more controlled operative environment but also reduced the need for exogenous blood transfusion by more than 30 per cent. During cross clamping of the inferior vena cava close monitoring of cardiac output, biochemical changes (in particular potassium and ionized calcium) and renal function was maintained. A fall in cardiac output may occur as a result of a fall in ionized calcium[23]. This is due to an acute citrate toxicity resulting from exogenous blood transfusion at a time when citrate cannot be metabolized by the liver.

Postoperative management protocol

Following transfer from theatre to the intensive care unit, patients were maintained on elective ventilation until they were normothermic, hamodynamically stable and well perfused with satisfactory blood gases and urinary output. Patients were not isolated or barrier nursed. Intermittent mandatory ventilation obviates the need for muscular relaxation so that patients' cerebral status and responses could be assessed.

Because patients with decompensated cirrhosis before transplantation had often undergone a prolonged period of clinical deterioration and catabolism, nutritional support was instituted at an early stage in the postoperative period. This was usually established via fine bore nasogastric feeding tube which allowed full alimentary nutrition. It was rarely necessary to resort to parenteral nutrition. External feeding via the fine bore nasogastric tube was continued at night-time well into the postoperative period until full normal eating patterns were re-established using one litre supplements of Clinifeed.

Abdominal drains, urinary catheters, intravenous and intra-arterial cannulae were all removed as soon as possible to minimize risk of retrograde contamination and infection. The majority were removed within 48 h of surgery and patients were transferred from intensive care to the main liver unit as soon as possible thereafter. The mean time in intensive care was 7 days. The biliary T-tube remained on free drainage for a 10 day period and was irrigated twice a day with 10–15 ml normal saline. On the tenth postoperative day a T-tube cholangiogram was performed and if there was no significant leakage or obstruction the tube was clamped, returning bile to the gastrointestinal tract.

Immunosuppression

Patients were initially treated with hydrocortisone 100 mg b.d. intravenously and azathioprine 1·5 mg/kg bodyweight daily orally. If adequate renal function was established and the patient was haemodynamically stable, but not taking oral fluids and medication, intravenous cyclosporin was given twice daily by slow infusion with a total daily dose of 5 mg/kg bodyweight for a 48 h period, before introduction of oral cyclosporin. Whole blood trough levels of cyclosporin were measured using a radioimmunoassay technique[24], although these were not immediately available to assist clinical management.

Protocol liver biopsies

Liver biopsies were performed on a protocol basis 7 days postoperatively and at 28 days if the patient was still an inpatient, or sooner in the case of hepatic dysfunction.

Results

By May 1986 50 orthotopic liver transplants had been carried out in 46 patients (4 regrafts). Thirty-one patients were operated on because of chronic end stage liver disease, thirteen for primary hepatic malignancy (either multicentric within the liver or secondary to cirrhosis and therefore unresectable) and two for fulminant liver failure. Twenty-seven patients are alive, and sixteen have lived longer than one year. The mean time spent in hospital in the first year for those living 12 months was 47 days (22–88) and 27 days (1–92) for those patients who died in the first year. All patients have now been followed up for a minimum of 3 months.

Postoperative complications were defined as those occurring during the main hospital admission and have been classified as severe, moderately severe or mild. Severe complications have been defined as those which required operative intervention or led directly or indirectly to the patient's death in the postoperative period (*Table 1*). Sixty per cent of the patients in the postoperative mortality group had more than one of these complications. Moderately severe complications were defined as those requiring non-operative treatment and not directly resulting in postoperative death (*Table 2*). Mild complications (*Table 2*) did not require active clinical therapy and included pleural effusions (33), and bactibilia (38).

Severe complications

Deaths (Table 3). Following liver transplantation there were three deaths within 48 h of surgery (6·5 per cent) and a further eleven deaths (23·9 per cent) by 30 days after surgery. One patient died at 42 days.

There were four deaths outside the postoperative period. Two patients died from recurrent hepatoma at 4 and 10 months, one patient from chronic rejection at 5 months, and one from graft necrosis and Herpes zoster infection at 4 months.

Two patients died within 48 h of surgery as a result of continuing operative haemorrhage (OL 13 and 28). They had both had previous upper abdominal surgery. Four further patients, in whom the initial major problem was severe per- or postoperative bleeding, had a slightly longer postoperative survival but died from a combination of factors including opportunistic infection (OL 1, 11, 12 and 20). OL 11 and 20 had

Table 1 *Severe complications: postoperative complications leading to death or re-operation*

Complication	Number of patients	Percentage of transplants	Mortality (%)
Severe bleeding	9	18	89
Renal failure	10	20	80
Opportunistic infection	6	12	100
Graft necrosis	9	18	78
Biliary leak	4	8	0
Biliary obstruction	2	4	0
Chronic rejection	4	8	25
GI bleeding	4	8	50
Pancreatitis	2	4	100
Small bowel obstruction	1	2	100
Perforated duodenum	1	2	0
Secondary haemorrhage	1	2	100

60 per cent of patients dying had more than one complication

Table 2 *Moderately severe and mild complications*

Complication	Number of patients	Percentage of transplants
Acute rejection	30*	64
Chest infection	27	54
Cholangitis	11	22
Abdominal abscess	5	10
Neurological	11	22
Vertebral collapse	1	2
Bactibilia	38	76
Pleural effusion	33	66

The majority of patients have bactibilia and pleural effusions, which did not usually require active treatment (see text).* 32 livers

Table 3 *Postoperative and late deaths*

Main cause of death	*n*	Time (days)
Bleeding	2	1
Bleeding and opportunistic infection	4	24 (14–42)
Bleeding and graft ischaemia	1	12
Opportunistic infection	1	27
Graft ischaemia	3	9 (4–18)
Metabolic	1	17
Pulmonary oedema	1	0
Secondary haemorrhage	1	4
Pulmonary embolism	1	20
Graft infarction and Herpes zoster	1	133
Chronic rejection	1	144
Recurrent tumour	2	225 (143–307)
Total	19	

also had previous upper abdominal surgery. One patient with fulminant hepatic failure died on the table from a concurrent haemorrhagic pulmonary oedema in spite of successful grafting (OL 14).

Four patients died because of graft infarction in the postoperative period. OL6 had severe aortic valve disease and died from graft infarction at 4 days. OL40 died 6 days after retransplantation for graft failure, OL44 died 12 days after transplantation for sclerosing cholangitis with an acute Budd–Chiari syndrome involving the transplanted liver and OL45 died on day 7 from graft failure, but with multiple other problems.

OL30 died at 17 days from a combination of metabolic factors including renal failure and, terminally, pancreatitis. OL31 died 4 days postoperatively from a secondary haemorrhage from the inferior vena cava. In addition to liver disease she suffered from pseudoxanthoma elasticum, which may have contributed to her sudden bleed. OL36 died with multiple system failure, but the principal problem at the time of death was widespread fungal infection. OL47 had a cardiac arrest at 10 days, and was brain dead after resuscitation. Post-mortem examination revealed a small pulmonary embolus as the only obvious cause.

Bleeding. Severe peroperative blood loss has been defined as that requiring more than 70 units of blood at operation. This occurred in nine patients, of whom eight died in the postoperative period. In these cases haemorrhage from the undersurface of the diaphragm and the right adrenal area could not be controlled entirely by diathermy or suture ligation of bleeding vessels. Large abdominal packs were placed under the right hemidiaphragm in order to try to establish haemostasis in six patients. Two patients (OL13 and 28) died before packs were removed, and 4 (OL1, 11, 20 and 44) had them taken out at subsequent laparotomy. All these patients subsequently died in the postoperative period of multi-system failure. Two patients required a second laparotomy for control of bleeding. OL8 subsequently made a full recovery, but OL12 eventually died from a combination of renal failure and opportunistic infection. OL47 was closed without drains, and internal tamponade appeared to create effective control in this patient. Her death was not related to the severe bleeding.

Five of the nine patients had had previous surgery (vagotomy and pyloroplasty, open liver biopsy, splenectomy, attempted tumour resection and hepaticojejunostomy). One other patient in this group had dense adhesions over the liver, presumably as a result of a haemorrhagic liver biopsy. In addition to these five patients, there were three patients who had had previous surgery (minilaparotomy and liver biopsy, cholecystectomy and total colectomy) and who did not have problems with major haemorrhage. In total, therefore, five out of eight patients (62·5 per cent) having had previous upper abdominal surgery developed severe bleeding with a 100 per cent mortality.

Five of the nine patients in the severe bleeding group developed renal failure, and all these patients died in the postoperative period.

Renal failure. There were ten episodes of acute tubular necrosis and renal failure after surgery with the patients requiring haemodialysis. Eight patients died before renal function recovered. In five the cause of renal failure appeared to be major peroperative bleeding and hypotension (OL1, 11, 12, 20 and 44). OL30 had poor renal function pre-operatively due to progressive liver failure with a bilirubin of $>700\,\mu$mol/l. She developed anuria during an uncomplicated operation, despite adequate fluid, mannitol, frusemide and dopamine. She died with pancreatitis and marked acidosis and hyperkalaemia, despite haemodialysis, 17 days after surgery. OL36 was anuric before surgery and was established on dialysis for acute tubular necrosis before operation. OL40 had good renal function immediately after transplantation, but developed acute tubular necrosis in conjunction with graft failure as a secondary event. She died 6 days after retransplantation without any improvement in renal function.

Two patients (OL10 and OL15/17) recovered renal function after a period of haemodialysis and survived the first 30 days. They were both deeply jaundiced pre-operatively (bilirubin >400 and $500\,\mu$mol/l) and a right nephrectomy had been performed on OL10 in the course of the liver transplantation to control haemorrhage. OL15/17 developed renal failure during her second transplant for chronic rejection. She was the only one of this group to survive beyond 6 months and remains alive at more than one year. There was thus an 80 per cent mortality in the renal failure group, but if this was secondary to major peroperative blood loss, there were no survivors.

Opportunistic infection. Five patients (OL11, 12, 20, 36 and 40/42) died as a result of fungal infection and one died from septicaemia (OL1). This represents 10·8 per cent of all patients and 27·8 per cent of deaths. They had all received 3 day courses of high dose steroids (prednisolone 200 mg or methylprednisoline 1 g) as treatment for clinically diagnosed acute rejection and three were in the severe bleeding group. The diagnosis of fungal infection was made at post mortem in these three cases with aspergillus and candidal infection discovered at multiple sites. OL36 developed small bowel obstruction, secondary to fungal infiltration of the ascending colon. He was treated with parenteral amphotericin for widespread candidiasis, but died 3 weeks after transplantation. All patients in this group developed renal failure either postoperatively or as a terminal event.

Opportunistic cytomegalovirus infections have not been a major problem, unlike other series[25]. OL12 had a leucopenia diagnosed by bone marrow biopsy as cytomegalovirus induced and the virus was also cultured from the liver at post mortem. Cytomegalovirus complement serology monitoring has been performed in all patients, and only three of these were converted from negative to positive (OL19, 35 and 49). OL35 developed changes in liver function together with a rise in cytomegalovirus titres. Although cytomegalovirus hepatitis has not been proved on biopsy, this remains a likely diagnosis.

OL38 developed a severe Herpes zoster infection at 4 months affecting the left T_{10} dermatome. This was associated with a large intrahepatic abscess which was secondary to graft ischaemia.

Graft infarction. Nine patients developed graft necrosis. Seven patients died as a direct or indirect result of this, six in the postoperative period. Four patients had massive necrosis. OL6 had severe aortic valve disease and poor graft perfusion. OL40, after an initial satisfactory recovery and an episode of rejection treated with high dose prednisolone, had a massive necrosis at 9 days. Emergency coeliac angiography revealed a patent arterial anastomosis but poor arterial flow because of intrahepatic extrinsic small vessel compression. She was retransplanted but died 6 days later without regaining conciousness. Examination of the removed liver confirmed oedema and haemorrhagic necrosis, but no obvious cause, with the hepatic artery and portal vein remaining patent. While the cause of graft failure remains uncertain, acute rejection may have been the underlying cause. OL44 developed thrombus in the inferior vena cavae of the transplanted liver and an acute Budd–Chiari syndrome, leading to massive necrosis and death. OL45 never recovered from a technically satisfactory operation. Her aspartate aminotransferase levels increased suddenly at 5 days, and she died from multiple complications, including gastrointestinal haemorrhage. Consent for post mortem was not obtained.

Two patients (OL1 and 20) were found to have partial infarction at post-mortem examination, with fungal infiltration of the latter. Both these patients had severe bleeding at laparotomy and episodes of hypotension.

Two patients, currently alive more than 5 months after transplantation (OL39 and 41) were found to have ischaemic livers. These were shown to be ischaemic on technetium colloid isotope scanning, and subsequent angiography showed the hepatic artery to be thrombosed. They are clinically well, although with deranged liver function. OL38 died at 4 months, as previously described, after developing an infarcted area secondary to arterial thrombosis in the fifth week after grafting.

Biliary complications. Four patients in this initial series had significant bile leaks, necessitating surgery. OL4 required re-exploration 12 days after transplantation for a biliary leak. Following closure of the leak site, she made a good recovery despite requiring two courses of high dose steroids for acute rejection. She remains well more than 2 years after transplantation. OL9 required a laparotomy on day 7 for repair of the biliary anastomosis. A further return to theatre was necessary at 15 days for the closure of a duodenal perforation. Unfortunately he died from recurrent malignant disease at four months.

OL35 had her T-tube removed at 6 weeks because of partial obstruction at the lower anastomosis. She developed a minimal leak, followed by intra-abdominal abscess formation. This was initially treated by ultrasound guided drainage, but eventually formal surgical drainage was required at 100 days.

OL39 developed a biliary leak from the T-tube site which required exploration 14 days after transplantation (*Figure 4*). This was associated with graft ischaemia. OL3 had radiological evidence of a leak on T-tube cholangiography, but because she had no clinical signs she was treated conservatively. One month later this leak had sealed.

OL7 was re-explored 5 days after transplantation because of biliary obstruction. At laparotomy the T-tube was found to be blocking the common bile duct. This was repositioned in the gallbladder without splinting the anastomoses, relieving the obstruction. She made good progress and remains well 22 months later.

OL49 required reconstruction of the bile duct one month after grafting. He had a narrow recipient duct and, although a primary anastomosis was performed at transplantation, subsequent Roux-en-Y formation proved to be necessary.

Duodenal ulceration. Apart from the one patient already described, there were no other episodes of perforated peptic ulcers. Gastrointestinal bleeding from peptic ulceration has not been a major problem. One patient (OL33/37) developed melaena due to ischaemic colitis following retransplantation, which settled on a conservative treatment. OL38 had one episode of melaena due to an oesophageal ulcer and two patients (OL44 and 45) had gastrointestinal bleeding as a terminal event.

Pancreatitis. Two patients developed pancreatitis (OL30 and 36). This was a terminal event in each case and was associated with multi-system failure.

Abdominal abscesses. Five patients have had intra-abdominal abscesses. These were associated with perforated duodenum (OL9), biliary leak (OL35) and graft ischaemia (OL38 and 39). OL29 developed a subhepatic abscess which presented one month after retransplantation. Gram-negative organisms were cultured on drainage. All but the first were treated by ultrasound guided drainage and insertion of pig-tail drains.

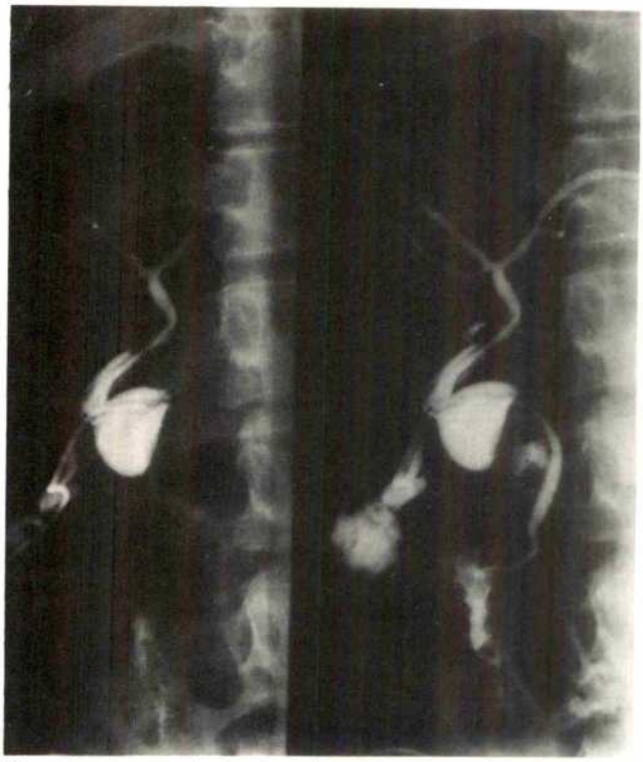

Figure 4 *An example of contrast leaking from the reconstructed biliary system following transplantation. This patient required re-operation*

Table 4 *Re-operation after transplantation*

Operation	Number	Mortality
Removal of packs	4	4
Exploration for bleeding	2	1
Biliary obstruction	2	—
Biliary leak	3	—
Biliary leak + duodenal perforation	1	—
Small bowel obstruction	1	1
Regrafting	4	1
Total	17	7 (41·2%)

Wound infections have not been a common problem, occurring in only one patient, OL9, after drainage of the subphrenic abscess following duodenal perforation (q.v.).

Moderately severe complications

Rejection. Thirty of the forty-two patients (71 per cent) living beyond 7 days had at least one episode of rejection and two of the retransplanted livers have also undergone rejection. Rejection is defined as a clinical or biochemical deterioration which responds to increased steroids, and by histological criteria. Initially liver biopsies were only performed at subsequent laparotomy, but since OL15 all episodes of hepatic dysfunction have been histologically evaluated and rejection confirmed using Menghini needle biopsies of the liver. The histological features of acute rejection are described in detail elsewhere[26]. Those consistently present are portal tract inflammation and polymorphnuclear inflammatory infiltration of the biliary epithelium. Four patients progressed to chronic rejection; OL10 died at 5 months. Three patients were successfully retransplanted, OL15/17 at 2 months, OL29/34 at 3 months and OL33/37 at 40 days.

Three patients were not treated for rejection, two because of mild changes only which settled spontaneously, and one because the patient was moribund. The other 27 have been successfully treated by short courses of increases in steroids (typically 200 mg prednisolone for 3 days). The first alteration in liver function tests in these patients occured between 3 and 13 days. The most common presentation was a rise in alkaline phosphatase and bilirubin levels, followed by a rise in aspartate aminotransferase some days later. *Figure 5* demonstrates the typical appearance of the liver function tests in rejection, when plotted logarithmically.

Two patients had acute rejection diagnosed and treated on clinical grounds, although the diagnosis was later found to be wrong. OL12 developed a rise in all three liver function tests 6 days after orthoptic liver transplantation. A wedge liver biopsy, performed at day 4 when abdominal packs were removed at laparotomy, did not show typical features of rejection. She was treated for clinically diagnosed rejection from day 8 onwards, but the liver function tests continued to deteriorate, and she developed a leucopenia. She died 24 days after transplantation from a fungal septicaemia, graft ischaemia and a cytomegalovirus hepatic infection.

One patient (OL20) was treated for a clinically diagnosed episode of rejection, when his liver function tests deteriorated at day 8. Poor clotting precluded biopsy at this stage, although a wedge biopsy carried out 3 days after transplantation showed centrilobular necrosis compatible with ischaemic damage and portal inflammation consistent with acute rejection. He died at 15 days and the post-mortem examination revealed large areas of infarcted liver colonized with *Aspergillus*. There was no histological evidence of rejection at this time.

Cholangitis and bactibilia. Thirty-eight patients in all, including all but one of the patients living more than 30 days, eventually developed positive bacteriological cultures from bile aspirated from the T-tube. The pattern was similar in most cases, with the first isolated organisms being *Micrococcus* (*Staphylococcus albus*) or *Streptococcus faecalis* and thereafter increasing to include a range of organisms, including bowel flora. The variety and type of organism cultured and isolated bore no general correlation with clinical events and we regard them as organisms colonizing the T-tube and the biliary tract in the presence of a foreign body. Eleven patients, (OL3, 8, 9, 22, 29, 35, 38, 39, 41, 48 and 49) were diagnosed as having cholangitis, which responded to antibiotics. Antibiotics are also used when there is hepatic dysfunction which has not yet been confirmed as acute rejection. Appropriate antibiotics are used prophylactically before T-tube cholangiography.

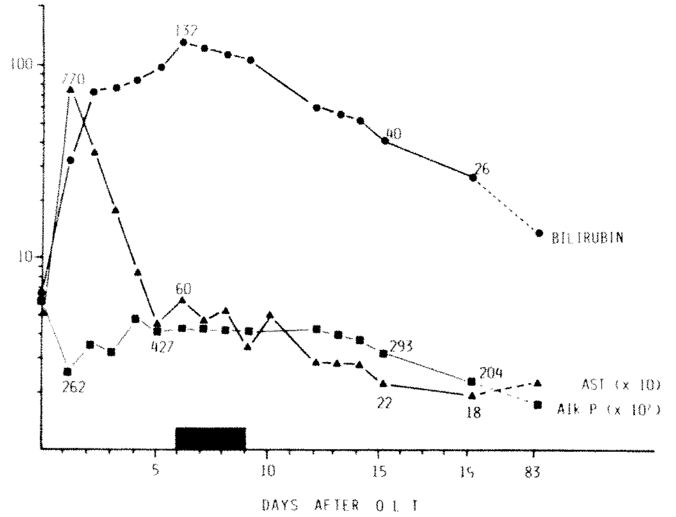

Figure 5 *Biochemical liver function tests in acute rejection (patient OL25). This graph shows the liver function tests plotted logarithmically for the first 14 days after liver replacement. OLT, orthoptic liver transplantation;* ●, *bilirubin;* ▲, *aspartate aminotransferase* (× *10);* ■, *alkaline phosphatase* (× 10^2). *Because of rising alkaline phosphatase and bilirubin levels, a biopsy was performed on day 6 which demonstrated acute rejection. This was treated with a 3 day course of high dose steroids (days 6–9) with a resultant improvement*

Biliary sludge. Only one patient (OL29) developed secondary biliary sludging at $2\frac{1}{2}$ months. This was associated with cholangitis and chronic rejection. There were no cases of primary biliary sludge formation.

Haemobilia. OL41 presented with blood stained bile 51 days after transplantation. T-tube cholangiography revealed thrombus in the common bile ducts and a fistula between the left hepatic duct and the hepatic venous system. Further studies have since shown her liver to be ischaemic from hepatic artery thrombosis, and this is almost certainly the aetiology of this complication.

Neurological complications. Eleven patients have had grand mal convulsions in the early stages of their postoperative recovery. (OL2, 5, 22, 24, 30, 34, 37, 40, 44, 47 and 49). These were all controlled by phenytoin and reducing the dose of cyclosporin, although this was only shown to be in high levels in two of the above. OL22 had a whole blood cyclosporin A trough level of 1764 mg/l on day 13, the day of her fit and OL34 had levels of 1122 mg/l on day 4, 24 h before her fit. This was associated with a pyrexia of 38°C. OL37 developed fits during a cyclosporin infusion, although trough blood levels were not above normal limits. Her serum magnesium was low at 0·51 mmol/l and needed correction. OL40 developed fits after retransplantation for graft necrosis, and at post mortem was found to have severe cerebral damage with infarction. OL44 developed fits whilst receiving cyclosporin. His ionized calcium levels were low, below 1 mmol/l, requiring constant correction with calcium chloride. No obvious cause has been found for the fits in OL47 and 49. Both were receiving cyclosporin A but had low blood levels together with normal calcium and magnesium levels.

OL10 presented with grand mal fits as a terminal event and at post-mortem examination had a cerebral haemorrhage.

Rhesus incompatability. OL50 developed generalized abdominal pains 6 days after transplantation. This was associated with a rise in total bilirubin levels from 270 to 1245 μmol/l in less than 24 h. More than 100 μmol/l was indirect bilirubin. Peripheral blood smears revealed the presence of spherocytes, and a direct Coomb's test was positive, indicative of severe haemolysis. She had been transfused with A positive blood despite being A negative because no blood of the correct group had been available and the cross match was normal. She required exchange transfusion with A negative blood and has subsequently made a rapid and uneventful recovery.

Chest problems. Although 40 patients developed chest problems, few were significant causes of morbidity. As a group, they were extubated at the earliest opportunity although one patient required a tracheostomy (OL1). Thirty-three patients had pleural effusions; twenty-two of these were right sided only, but eleven were bilateral. These appeared at a mean of 3 days with a range of 0–6 days. Only six of these patients (OL20, 33, 36, 38, 43 and 47) required drainage because of respiratory embarrassment. Thirty-three patients also developed radiological evidence of other pulmonary disease, which in the majority was self-limiting. Five patients developed a collapsed segment between 3 and 7 days and 27 patients developed an area of consolidation between 1 and 12 days. Two of these patients developed a significant chest infection. One was associated with a vertebral collapse and a fractured rib due to osteoporosis secondary to long term steroid therapy for primary biliary cirrhosis and OL42 died from an aspergillus pneumonia. One patient (OL8) developed changes consistent with adult respiratory distress syndrome by day 12. She had required re-exploration on day 2 and a further laparotomy on day 8 for removal of abdominal packs. She eventually made a full recovery and remains well more than 2 years later.

Discussion

The results detailed above demonstrate the difficulties experienced in the initial phase of the Birmingham liver transplantation programme, in which a large proportion of high risk patients have been included. Any unit considering the initiation of such a programme must therefore be prepared to face similar problems, and it is this aspect of hepatic replacement that usually determines any one hospital's response to the proposal from interested clinicians. Whereas some of these difficulties may be avoided by excluding high risk candidates, it is inevitable that there will be such problems when a full spectrum of liver disease is treated. The inclusion of children at an early stage in a liver replacement programme should not only improve overall results, but may also be associated with fewer postoperative complications[27]. The resources required for any centre considering the setting up of a liver transplant programme must be considerable, not only for the operation, which may often be the simplest part of the procedure, but also the complex postoperative care that is required[28].

Results of liver transplantation have improved considerably within the last 5 years. Before 1980 the Pittsburgh group were reporting a one year survival rate of 32·4 per cent; between 1980 and 1984 they were reporting one year survival figures of 68 per cent[11]. Cambridge, the other major pioneering centre, reported one year survival rates of 12 per cent before 1976, 32 per cent between 1976 and 1983 and 55 per cent since then[29]. The period since 1980 is commonly referred to as the 'post-cyclosporin era' but, although this drug undoubtedly has had an effect on patient survival, other factors should also be considered. There has been an increasing experience in the management of the patients pre-, per- and postoperatively and, as better results have been achieved, the referral pattern has changed, so that relatively fit patients are now also being considered for grafting. Indeed, it is now the policy of some groups to make the patients suitable for the operation by excluding those who are less fit and have increased risk factors. The indications for transplantation in some centres are thus the contra-indications in others. These factors include ascites, hypoproteinaemia and encephalopathy. A measure of selection is the high proportion of patients who are turned down as unsuitable[30–32]. Another major factor must be the increased use of retransplantation in the face of irreversible chronic rejection or early graft failure. This accounts for nearly 25 per cent of the transplants performed in Pittsburgh[19]. More children are now being transplanted for congenital biliary atresia, and their superior results are reflected in the overall totals[33].

Despite these improvements, many patients are still dying in the early postoperative stages and in our series 73·7 per cent of all deaths occurred within the first month. Most patients dying in the early stages after surgery do so because of technical complications – bleeding leading to renal failure, infarction or severe infection. Problems with the biliary anastomosis and acute rejection remain causes of significant morbidity (but rarely mortality now that low steroid schedules are employed) and yet the diagnosis of these is not always straightforward.

Bleeding has always been one of the major problems following orthotopic liver transplantation, and a major cause of mortality[4]. Our experience supports this evidence, as six of seven patients who needed packing or relaparotomy for severe peroperative bleeding (requiring more than 70 units) died in hospital. All patients developing renal failure as a direct result of bleeding died and, even though ultrafiltration and haemodialysis has been readily available, renal failure must be regarded as an additional grave prognostic factor.

Previous upper abdominal surgery was a risk factor for bleeding, although three patients who had undergone previous surgery did not have excess blood loss. One of the previous operations not resulting in adhesions had been a minilaparotomy at the referring hospital for histological biopsy, and the Cambridge team now perform a routine minilaparotomy in all non-cirrhotic tumour cases for staging purposes. They have not had serious problems as a result of this approach[21]. Another of our patients with previous surgery (total colectomy) had minimal adhesions but, more importantly, was a tumour patient without portal hypertension. The Pittsburgh group have reviewed their results in paediatric patients, looking at the effect of previous surgery on blood loss and mortality and morbidity. Although children who had failed Kasai porto-enterostomies had a greater blood loss and longer operating time, their mortality rate and time in hospital was similar to children without previous surgery[34]. We would now, however, actively discourage upper abdominal surgery in any adult patient under the age of 50 with hepatic disease until the case had been discussed with a transplantation unit. This is especially important in cirrhotic patients, and must include portosystemic shunting as a treatment for bleeding oesophageal varices or splenectomy.

Biliary problems, i.e. leakage or obstruction, were common in the early years of liver transplantation[16], and were described as the 'Achilles heel' of liver transplantation[8]. Choledochojejunostomies were commonly performed at this time, but better results are now achieved using either the gallbladder conduit method or a direct choledocho-choledochostomy. The Hanover unit[35] have described improved results with a side-to-side approach to this anastomosis rather than the conventional end-to-end approach. Most centres, apart from Cambridge, use the direct duct-to-duct anastomosis[36], except where problems with the recipient bile duct dictate the use of a choledochojejunostomy. Although our experience with these anastomoses has been satisfactory, we prefer the gallbladder conduit technique because not only is it simpler to perform the biliary anastomosis with the T-tube already in position but also there is never any tension on these anastomoses. The biliary complication rate has not been high in this series using this technique. There have only been four significant leaks and two obstructions.

Primary biliary sludging has not been a problem in our patients. Care is taken to flush the biliary system with preservation fluid before cold storage and transportation, because unprotected ischaemia has been shown to be a major cause of this problem[17]. The one case of sludging was secondary to cholangitis and chronic rejection. The T-tube was not flushed because of severe problems with ascending infection, and sludge appeared only after this change in management.

Graft infarction due to ischaemia had not been a frequently encountered problem in the first 3 years in this series, but we have recently had three patients with hepatic artery thromboses, two of whom are still alive. Routine arteriography is not part of our postoperative protocol, and it may be that this has been a hitherto unsuspected problem. Where protocol angiography has been performed in other centres, high rates of hepatic artery thromboses have been reported[37] and it may be that ischaemia is an underlying cause of cholangitis and biliary leakage. We are assessing the use of dynamic radioisotope scanning as a non-invasive indicator of graft vascular supply[38], and it may be that this will become a standard postoperative investigation in patients with hepatic dysfunction. Doppler ultrasound scanning has also been shown to be of benefit in determining the presence of arterial and venous thromboses. As a completely non-invasive investigation, this may be a method of demonstrating early vascular problems in time for corrective surgery to be undertaken[39,40]. Graft infarction in the presence of patent vascular structures is a difficult problem in terms of both diagnosis and treatment. This requires urgent regrafting. We have not been alone in seeing this problem.

While the role of the cross match in kidney grafting has come into question[41] and debate continues about the importance of tissue matching, there is no evidence to suggest that it is relevant in liver grafting[42,43]. Despite this, we have seen a high incidence of acute rejection, with 69 per cent of all patients surviving beyond 4 days having at least one episode of rejection. Thirty patients have had rejection, which was diagnosed either clinically or histologically. Acute rejection following orthotopic liver transplantation is notoriously difficult to diagnose by non-invasive means. The first 14 patients in this series were managed by clinical and biochemical assessment; percutaneous liver biopsies were not routinely performed during this period. Biochemical liver function tests have played an important role as an early warning system in alerting us when problems occur. Alkaline phosphatase and aspartate transaminase reflect a degree of hepatic damage, but display a low specificity, and it is impossible to predict whether a deterioration represents rejection, infection, ischaemia or biliary obstruction. Most episodes of rejection initially presented with a rise in alkaline phosphatase and bilirubin levels, closely followed by rises in aspartate aminotransferase levels in the majority of cases. Since OL15, liver biopsies have been used as an important part of the investigation of postoperative biochemical deterioration. These biopsies have been useful, not only in the initial diagnosis of acute rejection but also in subsequent management, where a biochemical improvement has not immediately followed a three day course of high dose steroids. In two such patients (OL21 and 22), biopsies taken after high dose immunosuppression showed resolution of acute rejection despite the lack of biochemical improvement. Further high dose therapy was thus avoided, on the basis of these findings. Both patients showed subsequent biochemical improvement and were therefore spared unnecessary high dose immunosuppression, which has been shown to be associated with a definite morbidity and mortality from fungal infection[44].

The main reason for the high incidence of acute rejection compared with other reported series may be our policy of low dose immunosuppression in these high risk patients. Some centres use high dose steroids as initial therapy, together with cyclosporin A given intravenously[45]. Our experience of giving this drug in the early stages has been associated with the initiation of grand mal fits. This has not been an isolated experience and has previously been reported in both renal and liver transplant patients[46–48]. Blood levels of cyclosporin are monitored by radioimmunoassay in all patients receiving this drug. We aim for whole blood levels of between 500 and 1000 mg/l. The complication of nephrotoxicity is well recognized in addition to the more rare complications of grand mal fitting already discussed. Because cyclosporin is a lipid soluble drug it has been suggested that larger doses are necessary when significant quantities of bile are lost, such as when the T-tube is on free drainage[49].

Upper gastrointestinal haemorrhage has been a rare complication in this series. It was a terminal event in two patients with graft failure and stopped on medical treatment in a third. The low rate compared to some other series[50] may be because of our policy of low immunosuppression, early enteral feeding and the use of routine prophylactic H_2 antagonists. Results from Groningen have also shown death secondary to duodenal perforation[25]. Only one patient in this series (OL9) had a duodenal perforation although there were no signs of mucosal ulceration. The perforation appeared to be secondary to operative trauma, either when peeling the tumour off the duodenum during the hepatectomy or at the second laparotomy.

Opportunistic infection is always a concern with immunosuppressed patients, particularly when the dose has been increased to treat episodes of rejection. Fungal infections, in particular, are associated with a high mortality[44]. In this series fungal infections followed the use of high dose steroids for suspected or proven rejection, haemodialysis for renal failure, and in three cases heavy peroperative blood loss. The deaths in these cases were multifactoral and the fungal infection was one of the terminal events. Fungal infection has not occurred in an otherwise well postoperative patient.

Our experience of 50 liver grafts in 46 patients suggests that despite the improvement in patient survival that has been reported since the introduction of cyclosporin A, the early postoperative period presents formidable problems in clinical management. While some patients have a relatively satisfactory and uncomplicated postoperative course, the high risk patient is in danger of developing a series of interacting complications which may prove difficult to manage. Severe haemorrhage leading to renal failure is almost always fatal, and previous upper abdominal surgery predisposes to this and is a major risk factor. We have not encountered many severe biliary problems. This has been achieved using gallbladder conduits, microvascular techniques and low dose steroids.

Rejection is no longer simply a diagnosis to be made by exclusion of infection, ischaemia or obstruction, but should be confirmed histologically before commencing high dose steroid therapy.

An awareness of the complications which may follow liver grafting enables the preparation of a careful approach to this phase of patient management. In spite of all difficulties, liver transplantation offers over 50 per cent of patients the chance of full rehabilitation from crippling and life-threatening disease with a prospect of a normal life style and full time employment, and, despite the difficulties in managing these complex patients, it must be regarded as a valuable weapon in the treatment of advanced hepatic disease.

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Colorectal cancer: the case for endoscopic screening

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The epidemic of colon and rectal cancer in the Western world continues unabated. In the last decade carcinoma of the colon has displaced gastric carcinoma as the most lethal alimentary malignancy[1]. Between 1946 and 1978 the increase in annual mortality from the disease in Australia has been roughly exponential[2], and there is currently no evidence of any reversal in this trend. In the USA in 1980 there were approximately 114 000 new cases of colorectal cancer, and 53 000 deaths attributable to the disease[3]. Each year approximately 6000 new cases of large bowel cancer are diagnosed in Australia, and between 3500 and 4000 Australians die of the disease[2,4]; this figure will rise to nearly 6000 within 15 years if current trends continue[2].

Limitations in the treatment of established cancer

Therapeutic advances over the last 30 years have been conspicuously unsuccessful in improving the overall prognosis of the disease. Improvements in surgical techniques for resecting colonic and rectal carcinomas have dramatically reduced operative morbidity and mortality rates[5,6]; adequate mechanical cleansing of the bowel has allowed safe primary anastomosis in the colon and rectum by removing the risk of suture line dehiscence associated with faecal loading of the bowel[7,8]; appropriate perioperative antibiotic prophylaxis has reduced the unacceptably high incidence of abdominal wound infection formerly accompanying large bowel resection; and several technical innovations, including stapling instruments[9] and effective intra-operative irrigation of the obstructed colon[10] have contributed to an increase in the proportion of sphincter-saving operations for rectal carcinoma and to a marked reduction in the performance of temporary or permanent colostomies[11]. These advances have radically improved the safety and comfort of colorectal resection for the patient, but have not been attended by any improvement in overall long-term survival rates after potentially curative operations; the overall 5-year survival rate after 'curative' resection in specialist centres remains a disappointing 40 per cent[5,6,12], and in many less specialized institutions has been as low as 25 per cent[13] (possibly because non-specialist units treat a higher proportion of patients who are elderly or present either as emergencies or with advanced disease[14]).

Recent evidence suggests that increasing the extent of resection of large bowel carcinoma has little, if any, influence on survival rates[15,16]. Following initial optimism for cytotoxic chemotherapy or radiotherapy in combination with surgery to treat breast cancer[17–19], considerable attention has therefore been directed towards the possibility of improving the results of surgical resection of large bowel cancers by adjuvant chemotherapy or radiotherapy. Despite early studies which suggested a possible survival advantage in patients treated with pre-operative radiotherapy in addition to surgery for rectal carcinoma, however, the recently published report of the UK Medical Research Council Working Party on adjuvant radiotherapy with surgery for rectal carcinoma, representing the most comprehensive such study yet performed, failed to demonstrate any improvement in 5-year actuarial survival rates in patients receiving single – or multiple – fraction low dose pre-operative radiotherapy[23]. Postoperative adjuvant radiotherapy in a higher dose (4500 rad) is currently being studied by the Australian and New Zealand Bowel Cancer Group, whose results are not yet available, but a similar treatment programme in the study undertaken by the Gastrointestinal Tumour Study Group failed to influence interval to tumour recurrence unless combined with postoperative adjuvant chemotherapy (5-fluorouracil (5-FU) and methyl CCNU), when disease-free survival but not overall survival was significantly improved[24].

Similarly equivocal results have been reported from studies of adjuvant chemotherapy in patients having surgical resections for colonic or rectal tumours. Although a preliminary report from the United States Central Oncology Group suggested significantly better disease-free and overall survival by life-table analysis approximately 2 years after resection of rectal carcinomas in patients treated with adjuvant systemic 5-FU than in controls who had surgery only[25], these findings were not confirmed at 5-year follow-up by the Gastrointestinal Tumour Study Group, using adjuvant 5-FU and methyl CCNU[24]. The same group was unable to demonstrate any improvement in disease-free or overall survival at 5-year follow-up in patients with colonic carcinoma receiving adjuvant chemotherapy with 5-FU and semimustine in addition to conventional surgical resection[26]. Taylor *et al.* have demonstrated a significant improvement in overall survival rate after follow-up for more than 5 years in patients receiving portal vein cytotoxic perfusion with 5-FU after potentially curative resection of colonic and rectal carcinomas[27]. However the benefit in this study was mainly confined to patients with Dukes' Stage B lesions, whereas an earlier study by the same group demonstrated a similar advantage from adjuvant 5-FU mainly in patients with Dukes' C carcinomas[28]. These results therefore require corroboration, particularly in view of the potential toxicity of the agents used. It may be that cytotoxic agents more active against large bowel adenocarcinoma will have to be developed before any real benefit can be convincingly demonstrated from this type of therapy. Since patients dying from advanced colorectal cancer tend to do so from disseminated rather than from local disease it is certainly rational to suppose that some form of effective systemic adjuvant therapy could have a significant impact on mortality in the future[29].

Although at present primary definitive treatment of patients with colorectal cancer is less than ideal, potential for improvement in results may perhaps be discerned in two other aspects of the overall management of the disease. The first of these is the intensive follow-up of patients after potentially curative resection in the hope that early metachronous or recurrent disease can be detected in some cases when still amenable to potentially curative treatment. Unfortunately, evidence currently available suggests that aggressive follow-up of these patients with regular intensive assessment to detect early recurrence (including serial measurement of serum carcinoembryonic antigen levels) has little or no effect on long-term survival[30]. As yet however no detailed studies have been reported of the effect on mortality rates of two screening modalities which may have contributions to make in the follow-

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up of these patients: colonoscopy to detect metachronous second primary carcinomas (and occasionally local recurrences) at an early stage; and ultrasonic examination of the liver to detect solitary or limited hepatic metastases which may be amenable to resection with increasingly promising results[31–33]. These techniques may prove capable of salvaging a number of patients who would otherwise die of recurrent disease. However it is perhaps over-optimistic to hope that they could have a major impact on overall colorectal cancer mortality rates.

Primary prevention of colorectal cancer

As an alternative, prophylactic measures probably offer considerably greater potential for reducing the mortality of large bowel cancer. The association of colorectal cancer with environmental factors[4], particularly low dietary fibre[34] and high dietary meat and fat intake[35], suggests the possibility that a major modification of dietary habits in afflicted populations might make considerable inroads into the incidence of the disease. Unfortunately such dietary modifications, if effective, would probably have to precede any noticeable changes in colorectal cancer incidence by a lead time of several decades, and might merely result in the exchange of one gastrointestinal malignancy for another. In view of these drawbacks, primary prevention may be less attractive than secondary prevention by screening for asymptomatic early malignancy and premalignant disease.

Screening for premalignant conditions

Perhaps the most attractive target for screening programmes in this context is the premalignant polyp of the colon or rectum. Much of the circumstantial evidence suggesting that most if not all colorectal cancers arise in previously benign adenomatous polyps has been summarized by Muto *et al.*[36] as follows. (1) The increased risk of colorectal cancer in patients suffering from familial polyposis coli has been well documented; in addition the risk of carcinoma developing in these patients increases with increasing interval from the original diagnosis of polyposis coli. (2) When the incidence of colorectal polyps and cancers in a population is plotted against age, the curves for polyps and carcinomas are very similar, the peak in incidence of adenomas preceding that of carcinomas by approximately four years. (3) Patients with colorectal cancer frequently have benign adenomatous polyps elsewhere in the large bowel at the time of diagnosis of the index cancer. (4) In patients with adenomatous large bowel polyps who do not fulfil the diagnostic criteria for familial polyposis coli, the risk of developing overt colorectal cancer increases in proportion to the number of polyps present. (5) At 25-year follow-up, metachronous second primary cancers are more common in patients who had separate large bowel adenomas at the time of diagnosis of the index primary than in those who did not. (6) Elements of benign adenomatous tissue are detectable histologically in the periphery of about 14 per cent of carcinomas. (7) Epidemiological studies have demonstrated that populations with little or no risk of developing colorectal cancer (for example the Japanese and the South African Bantu) also have a very low incidence of large bowel polyps. (8) Areas of mucosal cellular dysplasia or carcinoma *in situ* have been identified histologically only in association with mucosal polyps, or in patients with idiopathic inflammatory bowel disease.

Several other histopathological studies have emphasized the close relationship between colonic adenomas and carcinomas. Different grades of cellular atypia can be identified in different adenomatous polyps, suggesting the possibility of a gradual transition from a totally benign to a frankly malignant lesion[37]; and in established rectal cancers, there is an inverse relationship between the persistence of recognizable adenomatous tissue and the invasiveness or degree of spread of the neoplasm[38]. Furthermore, the likelihood of cellular atypia or frank malignant degeneration in a large bowel polyp is directly related to the size of the polyp[39]; assuming that polyps arise as small lesions which get progressively bigger, it follows that the risk of carcinoma developing in a polyp depends on the length of time for which the polyp has been present. Finally, both separate benign adenomas and benign adenomatous tissue contiguous with malignant tissue are more commonly found in patients with multiple synchronous carcinomas of the large bowel than in those with solitary primary cancers[40].

If the initially benign adenomatous polyp is indeed the predominant precursor of colorectal cancer, the natural history of this disease is unusual in that it has a relatively prolonged premalignant phase which is macroscopically recognizable and eminently amenable to detection and removal by currently available techniques. There is evidence that screening programmes for detecting early breast cancer can reduce cancer specific mortality in screened populations[41] – yet breast cancer, unlike colorectal cancer, demonstrates no such recognizable premalignant phase. Colorectal cancer may thus prove even more suitable for appropriate screening programmes.

Screening for early malignancy

Detection of faecal occult blood

Until recently most attempts to screen populations for early large bowel neoplasia have relied on the detection of occult blood loss in faeces. The Hemoccult test has been extensively assessed for this purpose. The test itself is relatively inexpensive (although follow-up investigations in patients who are Hemoccult positive add considerably to the overall cost of Hemoccult screening programmes[42]); patient compliance may be as high as 70 per cent in well motivated populations[43–45]; occult blood screening programmes do uncover asymptomatic colorectal cancers in up to 0·3–0·5 per cent of patients screened[43,44]; and most of these cancers are discovered at an early pathological stage[43,44]. Unfortunately, owing to lead time and length biases, earlier disease detection may suggest improvements in survival rates which are more apparent than real[42]. Only three studies[46–49] have attempted to deal with the problems of lead time and length bias by comparing overall and cancer-specific mortality in screened populations with similar parameters in control groups, and the definitive results of these are as yet unavailable. Hemoccult testing may be fundamentally limited by its relative insensitivity and lack of specificity as a predictor of colorectal neoplasia[50–53]. The effectiveness of immunochemical[54,55] or fluorimetric[56] techniques in improving the predictive value of occult blood screening has yet to be demonstrated[42,57,58], possibly because blood loss in the faeces, even when overt, is inherently a poor predictor of colorectal neoplasia[59].

Endoscopic and radiological screening

It is therefore appropriate to consider whether alternative screening modalities might be capable of improving the overall efficacy and cost-effectiveness of screening programmes in reducing colorectal cancer mortality. Considerable attention has been directed towards the use of endoscopic techniques in such screening programmes, particularly in view of the increasing availability of fibreoptic instruments for visualization of the colonic lumen. In the study of Rozen *et al.*, fibreoptic sigmoidoscopy proved approximately twice as sensitive as Hemoccult screening in detecting colorectal neoplasms in asymptomatic subjects[60]. Other investigators have confirmed that fibreoptic sigmoidoscopy appears a more effective screening modality for colorectal neoplasia than faecal occult blood testing or rigid sigmoidoscopy[61–63]. In several series fibreoptic sigmoidoscopy has been shown to be a practicable out-patient procedure which detects colonic neoplasms in as many as 10 per cent of asymptomatic individuals screened[64–66] (17·5 per cent in one study[67]); furthermore this form of screening does not necessarily require the direct participation of medically qualified personnel[66]. Unfortunately its ability to affect colorectal cancer mortality may be limited by the apparent shift in the distribution of colonic cancers from the left towards the right colon in recent decades[68,69]. The fibreoptic sigmoidoscope cannot reach and therefore cannot screen the proximal colon; it is thus likely to be less sensitive than procedures which allow effective examination of the whole colon.

Only two such techniques are currently available – colonoscopy and the double contrast barium enema. There has been some controversy as to which of these techniques is the more specific and sensitive in detecting mucosal abnormalities of the large bowel. Perhaps not surprisingly, endoscopists have tended to favour endoscopy[70–72], while radiologists have preferred barium studies[73,74]. Although neither technique is perfectly sensitive in detecting colonic neoplasms, the majority of comparative studies have shown endoscopy to be slightly more accurate than double contrast barium studies[75–78]. In the hands of a competent endoscopist colonoscopy is neither more uncomfortable for the patient nor more time-consuming than a double contrast barium enema; moreover colonoscopy, unlike radiology of the colon, allows removal of early colonic neoplasms at the time of their diagnosis. Reservations about colonoscopy as a screening procedure for colorectal neoplasms thus centre on its cost-effectiveness in relationship to the risk of neoplasia in the screened population, and on adequate patient compliance.

Schapiro[79], analysing data obtained in a prospective study of routine colonoscopy in the pre-operative evaluation and postoperative follow-up of patients undergoing curative surgery for colorectal cancer[80], calculated that colonoscopic screening in this particularly high-risk group would cost approximately US$6000 more than radiological screening for each additional asymptomatic carcinoma discovered within 6 months of the initial operation. He considered this additional cost quite acceptable in view of the increased accuracy of colonoscopy and the presumed reduction in subsequent prevalence of advanced carcinomas whose treatment is very expensive. Other investigators have demonstrated a high yield both of additional neoplasms and of local recurrence in patients with colorectal cancer screened pre- or postoperatively by colonoscopy[81,82]. Colonoscopic screening in patients with previously treated adenomas is now considered sufficiently well established to justify prospective controlled trials designed to determine how frequently such screening examinations should be performed[83,84]; in the interim it has been recommended that these patients undergo colonoscopy approximately every 3 years[85,86].

Patient compliance

The issue of patient compliance in subjects not previously treated for colorectal cancer remains a major potential difficulty although the problem has been addressed in further studies of colonoscopic screening in other high risk groups. In a small group of patients with urinary diversion by ureterosigmoidostomy, compliance with a colonoscopic screening programme was 100 per cent, polyps being discovered in 41 per cent of the screened group and asymptomatic cancer in 6 per cent[87]. In kindreds manifesting the cancer family syndrome, only 45 per cent complied with colonoscopic screening; of these, 12 per cent had asymptomatic polyps and a further 4 per cent had asymptomatic carcinomas[88]. Since direct (autosomal dominant) inheritance of increased susceptibility to colorectal cancer may be more common than previously recognized[89], this group deserves particular attention. A compliance rate of 94 per cent has been reported in a study of colonoscopic screening after removal of colonic adenomas at St. Mark's Hospital[86].

The case for endoscopic screening

Necropsy studies in Scandinavia have shown that colonic adenomas are present in about one-third of unselected subjects, and increase in prevalence with increasing age[90,91]; in other populations it has been estimated that the prevalence of colonic adenomas is about 10 per cent in those aged over 40[92]. The risk of developing colorectal cancer is three times higher among near relatives of colorectal cancer victims than in the general population[93]. If most colorectal cancers do evolve from previously benign adenomas[36], then screening of these high-risk subjects by colonoscopy should produce a yield of neoplasms in around 30 per cent of those screened; (although it must be conceded that this figure represents a life-time risk of adenoma, and that the incidence of overt carcinoma will be much lower). The Gastroenterology Society of Australasia Study Group on Rectal Bleeding has concluded that screening for colorectal cancer is indeed justified in first degree relatives of colorectal cancer patients, although particular screening modalities have not been specified[94]. Colonoscopy has been described as the 'gold standard' of colorectal screening[42]; there are cogent reasons for testing its effectiveness as a screening modality in first degree relatives of colorectal cancer patients, particularly in those aged 45 or more. This should be done in the context of a randomized controlled clinical trial comparing long-term overall and cancer-specific mortality in the screened group with that in unscreened control groups.

In Australia, whose population in this respect is similar to that of Britain, Europe and North America, the overall mortality from colorectal cancer is approximately 26/100 000 population per year[2,4]. Over 95 per cent of these deaths occur in patients over the age of 45, and this age group constitutes only 30 per cent of the total population, so that the colorectal cancer mortality in Australians over the age of 45 is between 75 and 80/100 000 per year. The fact that this risk is increased by a factor of 3 in first-degree relatives of cancer patients[93] implies a colorectal cancer mortality in this group of approximately 240/100 000 per year. Based on these figures it can be calculated that a study designed to demonstrate a reduction in mortality at the 95 per cent confidence level with a power of 0·8 would require 7000 subjects in the screened group and 7000 in the control group for a 75 per cent reduction in mortality, 4400 subjects in each group for a 90 per cent reduction in mortality, or 3300 subjects in each group for a reduction in mortality of 99 per cent[95,96]. If colorectal cancers do arise mainly in previously benign adenomas, detection and removal of all such adenomas in the pre-malignant phase might reasonably be expected to produce a reduction in colorectal cancer incidence and mortality of approximately this magnitude.

Cancer registries exist in several countries which could provide records of patients treated for colorectal cancer. Surviving patients and, where possible, relatives of deceased patients could be contacted by post and requested to provide details of first degree relatives on a confidential basis. As an alternative, first-degree relatives could be accrued in a prospective manner by obtaining appropriate details from patients about to receive treatment for colorectal cancer and from those being followed up after treatment. By these methods it should be possible to identify between three and four first-degree relatives for each patient[97]. These relatives could then be contacted and requested to provide data for a study of cancer incidence: responders would be randomly allocated either to a control group or a study group either as individuals or in family groups. The control group could receive no screening, but would be contacted at the end of a 6-year study period to determine the incidence of mortality from colorectal cancer in the group. Alternatively, if ethical considerations precluded the use of a completely unscreened control group, these responders could be invited to participate in a Hemoccult screening programme. The incidence of mortality from colorectal cancer in the control group at 6 years could be compared with the same parameters in the study group, to determine whether invitation to participate in a colonoscopic screening programme had any demonstrable effect, and to minimize interval and lead time biases.

Responders in the study group would be invited to attend an interview at which the object of screening would be explained and an invitation extended to undergo colonoscopic screening. Those who agreed to participate in the screening programme would undergo colonoscopy with removal and histological examination of any mucosal abnormalities detected. Subjects in whom colonoscopy proved inadequate, either because the whole colon could not be examined or because of inadequate bowel preparation, should undergo double-contrast barium enema examination with further colonoscopy if this demonstrated any significant abnormality. After appropriate treatment of any invasive or *in situ* carcinomas, and eradication or exclusion of benign mucosal polyps, further colonoscopies could be carried out at 3-yearly intervals, a period chosen because studies of the life history of the adenoma–carcinoma sequence suggest that invasive carcinomas are unlikely to develop in previously normal mucosa in a shorter time[98]. The incidence of and mortality from colorectal cancer in this screened group at 6 years could be compared not only with the same parameters in the control group, but also with data obtained from subjects invited to participate in colonoscopic screening but refusing to do so. In this way the effect of volunteer bias could be assessed.

Such a trial would remain open until 7000 patients had been entered into the colonoscopic screening arm, or could be closed earlier if significant improvements in survival became apparent in the screened group. Given the high incidence of colorectal cancer in densely populated countries like Britain and the USA[3], this number of patients could reasonably be expected to accrue in an appropriately large population within a relatively short period; the factor limiting accrual rate would most likely be the resource base available to provide colonoscopic facilities.

If it is assumed that colorectal cancers would be detected in 10 per cent of the group screened by colonoscopy (a generous estimate), and further that these patients would require yearly colonoscopic follow-up after treatment of their carcinomas, the proposed study would generate between 23 000 and 24 000 colonoscopies over a 6-year period. If the Medicare Schedule fee for colonoscopy in Australia, $205 or approximately £100 sterling, is assumed to represent the cost of a colonoscopy (including the salaries of medical and other professional personnel involved), colonoscopic screening on this scale would cost roughly £2·5 million. Administrative expenses involved in data collection and recording would probably require additional expenditure of several hundred thousand pounds over several years.

The proposed study represents the most direct available method of testing the polyp–cancer hypothesis by determining whether colonoscopic screening has a major effect on the incidence of and mortality from colorectal cancer in the screened population. It would also provide answers to the clearly pertinent questions of patient compliance, cost-effectiveness and the morbidity and mortality of colonoscopic screening. Whether the information gained could justify expenditure of this magnitude is certainly a matter for debate: evaluation of the cost effectiveness of cancer screening programmes inevitably depends on the expectations and values of the society being studied[99].

It may well be that an initial pilot study should be carried out, involving a much smaller number of patients, to determine the frequency with which asymptomatic cancers can be detected in relatives of cancer patients and the cost of such a screening programme per cancer detected. The latter study would be much less costly than a full-scale prospective controlled trial, and, in possible contrast, seems clearly justified. However, there is no doubt that the cost of the larger trial would be well within the total health care budget of many affluent industrial nations.

It may well be argued that colonoscopic screening programmes would be too expensive to apply to the whole population at risk, even if the proposed study demonstrated that colorectal cancer mortality could be virtually abolished by so doing. The cost of such an exercise would certainly be formidable, but will be impossible to calculate effectively until or unless appropriate trials are undertaken. Colonoscopic surveillance of some relatives of colorectal cancer patients is already being carried out in the private medical sector in Australia, and possibly in some other countries; if the place of colonoscopy in screening for colorectal carcinoma is not adequately assessed by means of prospective, controlled trials within a few years, such trials may come to be regarded as ethically unjustifiable thereafter.

There can be little doubt that screening high risk groups by colonoscopy will reduce the incidence of colorectal cancer[98]. The extent of this reduction, and the justification or otherwise for including some family members of selected[100,101] or all colorectal cancer patients in the high risk category, can only be determined empirically. The University of Minnesota Cancer Detection Centre has shown the way ahead by demonstrating a dramatic reduction in the incidence of overt rectal carcinoma in a large group of unselected subjects screened periodically over several decades by rigid sigmoidoscopy with removal of all rectal polyps detected[102,103]. The parallel with fibreoptic screening of the remainder of the large bowel is clear; to paraphrase John Hunter's famous advice, perhaps we have now thought enough, and should try the experiment.

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Rising detection rate of symptomatic Dukes' A colorectal cancers

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All 197 patients admitted to the Bristol Royal Infirmary during the 16 year period 1970–1985, and diagnosed as having Dukes' A colorectal cancers, were studied. The numbers diagnosed per year by 1985 were 20, compared with 9·4 per year for the period 1970–1979. This represented an increase in the percentage of Dukes' A cancers of all the colorectal cancers diagnosed from 8·3 to 15 per cent. The increase was largely due to better quality double contrast barium enemas and increased use of flexible sigmoidoscopy and colonoscopy. The operative mortality dropped from 17 to 3 per cent in the last 6 year period. The recurrence rate was 9·6 per cent of which 1 per cent were locally resected and crude 5 year survival was 90·4 per cent up to 1981.

Keywords: Colorectal cancer

In the UK the overall 5 year survival from colorectal cancer is about 30 per cent and over 18 000 deaths per annum occur from the disease[1]. Survival after treatment for a Dukes' A cancer is over 90 per cent and yet these make up less than 6 per cent of all colorectal cancer patients diagnosed[2]. Delay in diagnosis is due to patient and doctor delay resulting from the non-specific nature of the symptoms and hospital delay in obtaining a positive diagnosis by appropriate investigation[3]. It has been suggested that, once colorectal cancer patients become symptomatic, earlier diagnosis does not necessarily improve the stage of the disease[4] and, as a result of this, emphasis has been placed on screening to detect asymptomatic cancers which may be earlier tumours[5].

During the past few years there have been improvements in barium radiology and lower gastrointestinal endoscopy has become more commonplace. The purpose of this study was to see whether these advances are making any impact on colorectal cancer detection and to assess the management of patients with early colorectal cancer.

Method

All patients diagnosed as having Dukes' A colorectal cancers during the 16 year period 1970–1985 were identified from the histological records at the Bristol Royal Infirmary. Follow-up information was obtained on all patients from hospital records and by personal review. Patients who had colonoscopic polypectomies were kept under regular review by colonoscopy while other patients were reviewed in ordinary surgical outpatient clinics with sigmoidoscopy, double contrast barium enemas, colonoscopy and latterly with rectal ultrasonography.

The original histology was reviewed by one pathologist (J.H.F.S.). Dukes' A classification was taken to be tumours confined to the bowel and not through the serosal layer as defined by Dukes in his original paper on carcinoma of the rectum[6]. Carcinoma *in situ*, without invasion, and severe dysplasia were not included as Dukes' A cancers.

Information regarding the total numbers of colorectal cancer patients diagnosed during the same period was obtained from the Hospital Activity Analysis, histology records and hospital discharge summaries.

Statistical analysis was performed using the χ^2 test for trend and the barium enema results were analysed using the χ^2 test for two proportions comparing 1970–1979 with 1980–1985 in relation to the number of enemas performed.

Results

A total of 197 patients (115 men, 82 women, mean age 66·7 years, range 18–92) were identified. The numbers detected per annum rose from 9·4 per year during the period 1970–1979, to 17·1 per year during 1980–1985 and 20 per year during the last 3 years of that period ($P < 0{\cdot}01$). Early colorectal cancers, defined as those limited to the submucosa with no muscle coat involvement, constituted 38 per cent of the total (*Figure 1*).

Active screening was undertaken in only one patient with a family history of polyposis coli though 26 patients were asymptomatic and diagnosed by chance and were evenly distributed throughout the years studied (*Table 1*). The remainder all had symptoms due to their tumours, the commonest being rectal bleeding. Predisposing conditions were present in 13 and consisted of previous polyps in 2, previous colorectal cancer in 5 (metachronous tumours), ulcerative colitis in 4, Crohn's colitis in 1 and polyposis coli in 1.

The method of diagnosis was by rectal examination or sigmoidoscopy in 104 (53 per cent), barium enema 53 (27 per cent), colonoscopy or flexible sigmoidoscopy 25 (12·5 per cent), laparotomy 8 (4 per cent) and incidental histology 7 (3·5 per cent). Incidental histological findings were where lesions were detected in specimens resected for complicated diverticular disease, colitis and in one case a man of 18 who was found to have carcinoma in his appendix which was removed for appendicitis. Laparotomy diagnoses were usually made when emergency surgery was required, there being four cases with obstruction. In the last 6 years barium enemas were diagnostic in about seven cases per annum with just under three per annum being on the right colon. Before 1980 the diagnostic

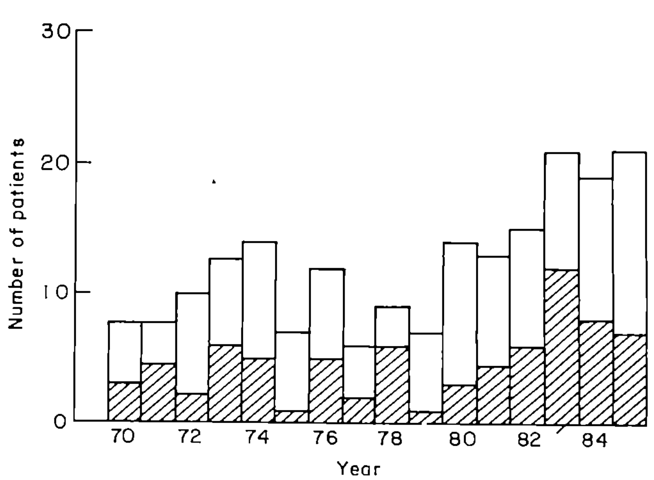

Figure 1 *Numbers of Dukes' A cancers diagnosed per annum.* ▨, *early cancers*

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Table 1 *Presentation of asymptomatic cancers*

Screening	1
Polyposis coli	1
Incidental	16
Diverticular disease	4
Ulcerative colitis	4
Crohn's colitis	1
Polyp at colostomy	1
Anaemia (carcinoma pancreas)	1
Post-vagotomy diarrhoea	1
Carcinoma follow-up	1
Appendicitis	1
Urinary retention	1
Pelvic inflammatory disease	1
Routine rectal examination	4
Hernia	2
Carcinoma prostate	1
Carcinoma breast	1
Sigmoidoscopy	5
Fissure	1
Polyp follow-up	1
Prolapsed haemorrhoids	1
Cirrhosis	2
Total	26 (13·2%)

rate for barium enemas was 1·3 per annum with less than 1 per annum being on the right colon. Overall barium enemas failed to detect 21 tumours, 18 during 1970–1979, and 3 during 1980–1985 ($P<0{\cdot}001$). *Figure 2* shows the sites of the lesions detected as well as those missed by barium enemas. Double contrast examinations became routine in 1979 and this corresponds with an increased detection rate of right sided lesions and decreased numbers missed by barium enema. Four tumours were detected by flexible sigmoidoscopy in a direct access clinic for general practitioners out of a total of 10 endoscopically detected tumours in the last 2 years. The majority of lesions missed by barium enema had been already detected by rigid sigmoidoscopy but those more proximal were usually detected by colonoscopy or repeat enema for persistent symptoms.

Thirty-six patients were treated by local per anal excision (twenty-three) or colonoscopic polypectomy (thirteen) though two had subsequent sigmoid colectomies as there was histological doubt about the completeness of the excision. Of these 36, 15 were treated in the last 6 years.

The overall hospital in-patient mortality was 19 (9·6 per cent) though this was 16 (17 per cent) for 1970–1979 compared to 3 (3 per cent) for 1980–1985. During the early period deaths were due to pulmonary embolus (five), bronchopneumonia (three), heart disease (three), hepatic vein thrombosis (one), iliac artery thrombosis (one), septicaemia (one), ischaemic colitis (one), and peritonitis (one). Between 1980 and 1985 the causes of death were due to cerebrovascular accident (one), myocardial infarction (one), and bronchopneumonia in a cirrhotic patient (one). A similar improvement in the overall mortality of all colorectal cancer patients was also noted with a drop to 6 per cent in 1984 (*Table 2*). However figures for every year were not available, so no statistical analysis could be performed.

Morphology of the tumours showed 125 (63 per cent) to be polyps or polypoid in shape, the remainder being ulcers of annular tumours. Only 3 (4 per cent) ulcer cancers were limited to the submucosa compared to 72 (58 per cent) of the polypoid tumours.

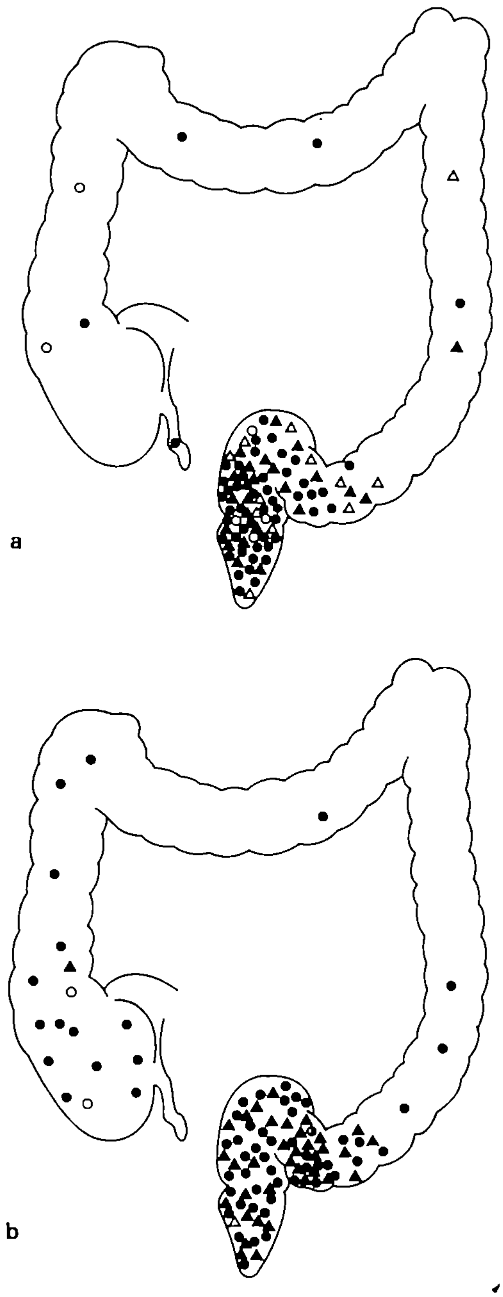

Figure 2 *Distribution of Dukes' A cancers* (**a**) *1970–9 and* (**b**) *1980–5.* ●, *Dukes' A;* ▲, *early cancers;* ○ △, *missed by barium enema*

Table 2 *Comparison of stage, mortality and emergency admissions between 1974 and 1984*

Dukes' stage	Percentage in 1974 ($n=120$)	Percentage in 1984 ($n=143$)
A	6	15
B	30	37
C	24	25
'D'	38	21
Not staged	2	2
Mortality	17	6
Emergency admission	31	23

There were 19 (9·6 per cent) cases of recurrent carcinoma, 9 with distant metastases and the remainder with local or pelvic recurrence. Only two cases were amenable to surgical resection, one with a curative result, and the other patient had an apparently curative response to radiotherapy there being no further problem at 6 years. Only two patients survived more than 5 years after developing recurrence. Review of the histology revealed one poorly differentiated tumour and three cases were deemed to be Dukes' B with spread through the serosa. One case was incompletely resected and in a further two the adequacy of the excision could not be assessed. Tumour was confined to the submucosa in two, circular muscle in seven and longitudinal muscle in five. Submucosal venous invasion was present in five and there was lateral submucosal spread in four.

In two cases of recurrence the tumour was breached during abdominoperineal excision of rectum and in one case on table lavage was carried out.

In those where no recurrence occurred, 17 were found to have penetrated deeply into the muscle layer and 6 were reclassified as being just Dukes' B. Of the nine Dukes' B lesions identified, five were between 1970 and 1979 and four between 1980 and 1985.

The corrected 5 year survival for all patients to the end of 1981 was 90·4 per cent. Over the same period there has been a slight increase in the overall numbers of colorectal cancer patients diagnosed from approximately 120 per year between 1970 and 1975 to 140 cases in 1985. There has therefore been an increase in the percentage of Dukes' A tumours from 8·3 to 15 per cent ($P < 0{\cdot}01$).

Table 2 shows a comparison of stage of disease, mortality and emergency admissions between the years 1974 and 1984.

Discussion

We have been encouraged by this study to see a genuine rise in the detection of Dukes' A cancers at the Bristol Royal Infirmary to a level of 15 per cent, a figure higher than most other published series in the UK[2,7] though this figure is still lower than that obtained from countries such as West Germany and the USA[8,9].

True early cancers with micro-invasion constituted only 38 per cent of all the Dukes' A cancers which is much lower than from other countries and for which there is no immediate explanation. The improved detection rate appears to be largely due to the routine use of double contrast barium enemas and the more frequent use of colonoscopy and flexible sigmoidoscopy. The number initially missed by barium enemas has been considerably reduced and, though it could be argued that missed lesions may be presenting later with more advanced tumours, there is no evidence to support this when barium enema results are followed up[10]. Previously it has been suggested that reducing delay in diagnosing colorectal cancer does not affect the stage of disease[4] but we believe our results now cast doubt on this. Four of the patients detected in the last 2 years presented to a direct access flexible sigmoidoscopy clinic set up to provide prompt investigation and reduce hospital delay.

The recurrence rate of 9·6 per cent is probably unacceptably high. In at least three cases the recurrence may have been due to contamination with viable exfoliated cancer cells[11] and vascular invasion and incomplete excision probably accounts for the reasons in the majority. Though it is too early to be certain, the recurrence rate has fallen in the last 5 years and this may be due to the routine use of cytotoxic washouts at the time of resection[12].

There has been a dramatic fall in the hospital mortality. The 17 per cent mortality from 1970 to 1979 compares with mortality for all those having curative resections for colorectal cancer up to 1975 of 17 per cent and 20 per cent when those that were non-curative are included[13]. The drop in mortality may be due to more interest in colorectal cancer by surgeons; improvements in anaesthetic techniques; the more frequent use of subcutaneous heparin to reduce the incidence of thromboembolic problems and the routine use of prophylactic antibiotics to reduce septic complications.

Though there has been an increased interest in colorectal cancer at the Bristol Royal Infirmary, we do not believe that this has altered referral patterns enough to explain the increase in early cancers detected, though it might explain the improved mortality and decreased number of emergency admissions. The trend appears to be more than random variation and is statistically significant, though we believe other centres should also look at their results to see if this is a general trend. Though we looked at many factors, the only ones we could find that appeared significant were the use of double contrast barium enemas and flexible endoscopy.

This study has demonstrated a doubling in the detection of Dukes' A colorectal cancers over the past 10 years. We believe that the liberal use of double contrast barium enemas and a vigorous endoscopic policy have been responsible for this increase. We predict that in due course an increased incidence of A cases will be reflected in better survival figures for colorectal cancer.

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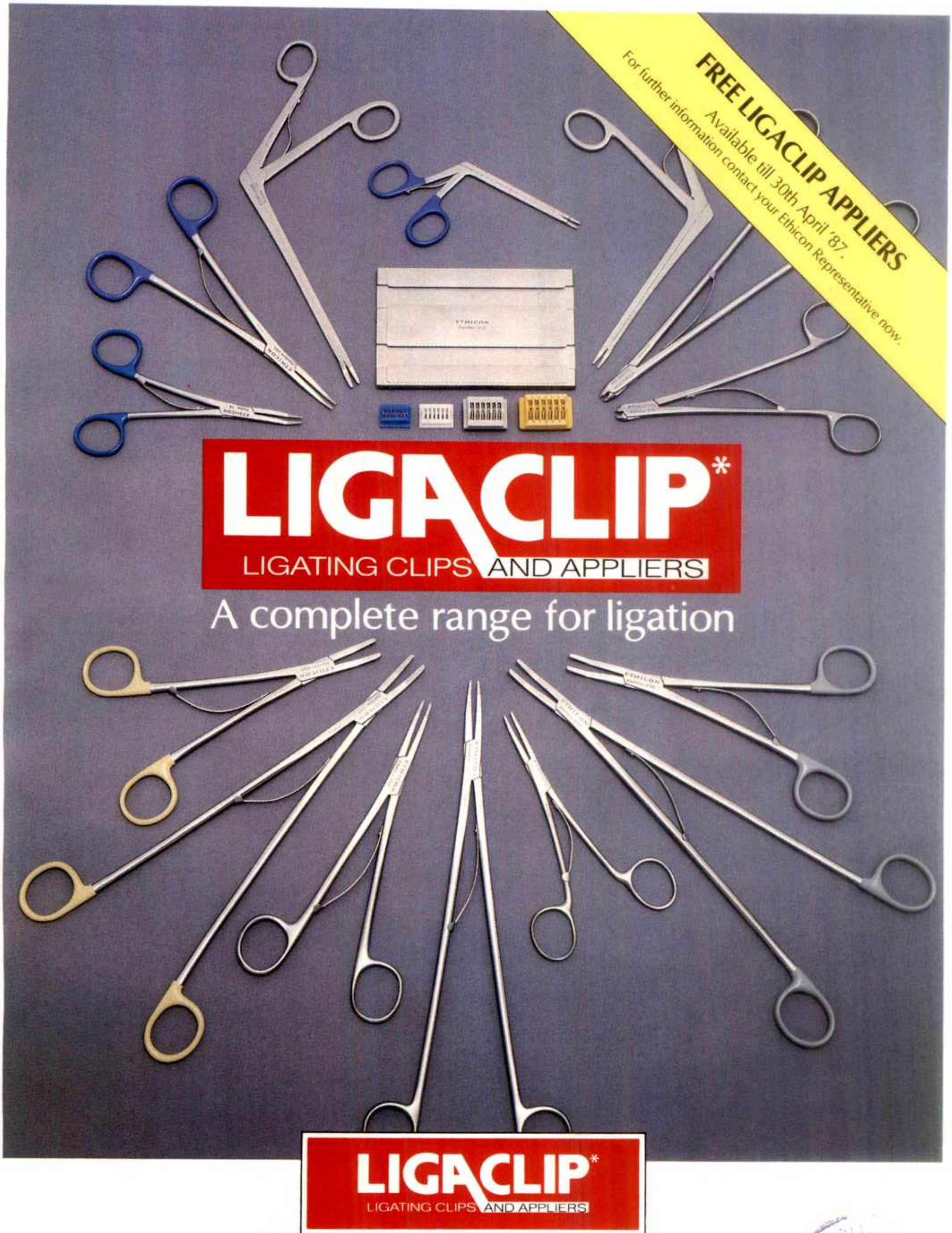
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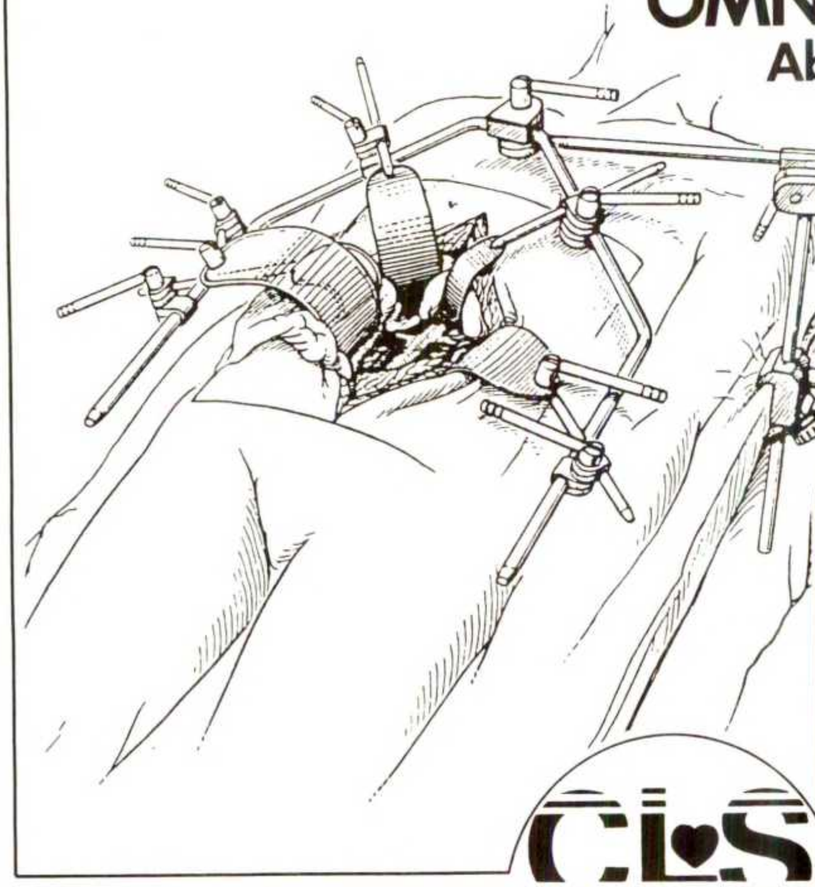

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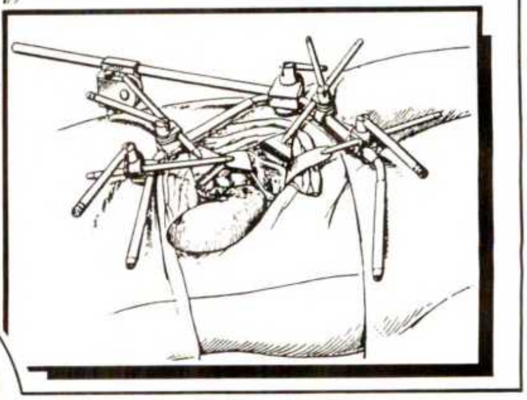

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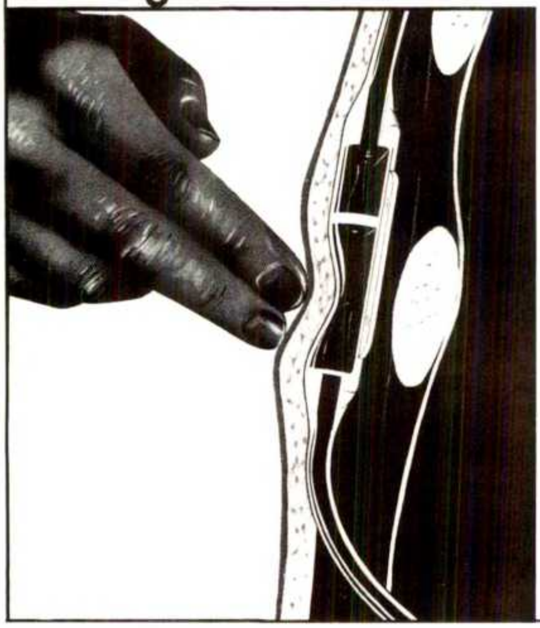

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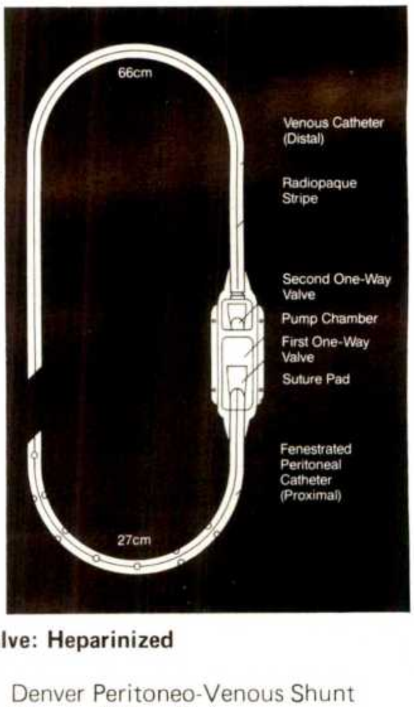

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Br. J. Surg. 1987, Vol. 74, January, 21-22

Dysplasia of the colon after jejuno-ileal bypass

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Colonoscopic biopsies were performed on 38 patients, 10–13 years after jejuno-ileal bypass. No significant dysplasia or premalignant change was seen in 371 biopsies. In one patient two tubulovillous adenomata were found in an otherwise normal colon, which is likely to be a chance finding. Although it will take another 10–20 years to establish whether jejuno-ileal bypass is associated with an increased risk of large bowel cancer in humans, there is at present no indication for regular colonoscopic surveillance.

Keywords: Colon cancer, colonoscopy, jejuno-ileal bypass, obesity

Small bowel bypass or resection consistently promotes the development of chemically induced large bowel cancer in animal models[1–4]. Williamson *et al.* have suggested this is a consequence of adaptive intestinal hyperplasia, which might be inhibited by profound weight loss[5,6]. Intestinal metaplasia occurs in humans after jejuno-ileal bypass for obesity[7,8] and it has been proposed that these patients may be at risk of developing large bowel cancer[9]. Jejuno-ileal bypass causes profound changes in transit times, bile salt metabolism, gut flora and dietary intake of fat, fibre and protein, all of which have been implicated in the aetiology of colon cancer[10–12]. Obesity itself is associated with an increased risk of colon cancer[13].

Since jejuno-ileal bypass was introduced in 1969[14], more than 10000 operations have been reported[15], a fraction of the total performed. Yet there are no reports of an increased incidence of cancer, adenomatous polyps, or even dysplasia in the colons of these patients. It is possible that insufficient time has elapsed for an association to have become manifest; the association between colon cancer and ulcerative colitis has a latent period of about ten years[16,17].

To address this problem we examined multiple colonic biopsies, obtained by colonoscopy, in patients 10–13 years after jejuno-ileal bypass. These patients were taken from a group of 187 in whom a jejuno-ileal bypass was performed at St. George's Hospital between 1971 and 1980, and who have recently been reviewed[18].

Patients and methods

Jejuno-ileal bypass was performed on 77 patients during 1971–75. All of these patients were invited to attend for colonoscopy to assess premalignant change in the colon. Thirty-eight patients agreed to be examined. The average interval since bypass was 11·5 ± 1·6 years (mean ± 1 s.d.) and the average age at examination was 50 ± 9·0 years. In four patients, the bypass operation left 18 inches of small intestine in continuity; in 34 a 14-inch bypass was performed. In nine of these patients the bypass had been reversed for complications after 3–10 years. The average starting weight was 126 kg (Body Mass Index 48 kg/m^2). At the time of colonoscopy the patients who were still bypassed had an average weight of 87 kg whereas all but two of those who had been reversed had regained their starting weight.

On the day before the examination the patients took three sachets of 'Picolax' at home and clear fluids only by mouth. After admission to hospital they were given a 'Veripaque' enema and colonic washouts until the effluent became clear. Colonoscopy was performed under sedation with intravenous diazepam (Diazemuls, Kabivitrum) and pethidine as necessary, using an Olympus LB3W colonoscope (Keymed).

Thirty-six patients were examined to the caecum and two to the hepatic flexure. Following insertion of the colonoscope, biopsies were taken of any macroscopically abnormal mucosa or randomly at approximately 10 cm intervals during withdrawal. Biopsies were mounted on card and immediately fixed in 10 per cent formal saline. Slides were prepared and stained with haematoxylin and eosin. Three hundred and seventy-one biopsies were examined for dysplasia, using the criteria usually applied to biopsies from patients with chronic ulcerative colitis[19].

Thirty-four patients provided specimens of stool for occult blood (Haemoccult) testing. Blood was taken for estimation of plasma carcino-embryonic antigen (CEA) and for metabolic screening.

Results

The colon was macroscopically normal in 37 of the 38 patients. One woman patient, 57 years old, had a polyp in the transverse colon and another in the rectum, both measuring less than 1 cm; these polyps were removed endoscopically. This patient had been bypassed in 1973 and reversed in 1979 when she developed osteomalacia. The two polyps were both tubulovillous adenomata, with some cellular atypia but no *in situ* malignant change. Another ten biopsies were taken from the same patient; six were normal but in four from the ascending and transverse colon some branching of the glands was seen.

No macroscopic lesions were seen in the other 37 patients, and the histology was normal in the great majority of random biopsies. Bifid or trifid glands were seen in eight biopsies from five patients. Attenuation of some of the crypts was seen in 17 biopsies from 8 patients with a reduction in goblet cells which were replaced at the base of the crypts by eosinophilic cells with central nuclei. These changes are minimal, and none of the features characteristic of dysplasia – pleomorphism, asymmetry, abnormal mitoses, tubular budding or abnormal cells in the upper tubule – were seen. Excepting the patient with polyps, nobody had more than two abnormal biopsies, and no particular region of the colon was affected.

Mucosal hyperplasia in response to the jejuno-ileal bypass was not seen, neither was it possible to distinguish histologically the patients in whom the bypass had been reversed. Crypt depth and cellular activity, as evidenced by the nuclear/cytoplasmic ratio and number of mitoses, appeared normal. However this was a subjective assessment only as the colonoscopic biopsies were too small to permit quantitative morphometry.

Occult blood testing was negative in all but one patient, who did not have a polyp. CEA was normal in all 28 patients tested.

Discussion

This study has failed to demonstrate any significant dysplasia or premalignant change in 371 colonic biopsies taken from 38 patients, 10–13 years after jejuno-ileal bypass. Hyperplasia of the colonic mucosa, as has been described in rats after jejuno-ileal bypass[5], was not seen in our patients, although colonoscopic biopsies do not permit formal morphometry. Neither could we distinguish the patients whose bypass had been reversed from those with a bypass intact.

It is likely that the two tubulovillous adenomata in the 57-year-old woman were a chance finding, particularly as her bypass had been reversed six years previously and as the rest of her colon was relatively normal with no evidence of 'field change'. After a latent period of only 10–13 years it is probably too soon to conclude that there is no increased risk of colon cancer after jejuno-ileal bypass; in patients with chronic ulcerative colitis the incidence of dysplasia is only 2·4 per cent at ten years although it increases to 19 per cent later[17]. An epidemiological study over the next 10–20 years may yet unmask an association between jejuno-ileal bypass and cancer of the colon.

Premalignant change has not been identified in the mucosa of patients and at present regular colonoscopic surveillance of

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these patients is not indicated. However, bypassed patients require regular follow-up and stool testing for occult blood, sigmoidoscopy and rectal biopsy could reasonably be included.

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Surgical workshop

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Omnitract retractor

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Self-retaining retractors suffer from several disadvantages. The equal and opposite reaction forces do not always afford optimal exposure. Furthermore rotational forces often allow the retractor to move through an arc. For approximately 6 months we have been using a new surgical retractor, designed for complex abdominal operations which require a large incision.

The retractor which we describe (Omnitract*) is particularly versatile. The Omnitract retractor framework consists of a wishbone-shaped yoke which is supported over the patient by vertical and horizontal rods secured to the operating table side-runner without disrupting the sterile field (*Figure 1*). The position of the yoke can be easily adjusted and a wide range of retractor blades is available, each of varying width and length. These are distributed around the yoke and secured in place with simple screw fittings. The main framework takes approximately 1 min to assemble. The patient being operated upon in *Figures 1* and *2* had a transverse incisional approach to an abdominal aortic aneurysm. The blades have been secured in position exerting firm retraction on the abdominal wall with swabs acting as cushions between more gentle blades and viscera (*Figure 2*). This excellent view is maintained throughout the operation. Lapses of an assistant holding a conventional retractor may produce periods of reduced retraction, and a theoretical risk of retraction derives from unremitting pressure on the retracted structures, including the heart and abdominal wall. However we have not experienced any complications to date. The various blades and framework can all be autoclaved although at present the yoke has to be sent to the larger central sterile supply department autoclave for sterilization. The manufacturer is designing a folding yoke to overcome this snag. The advantage of retraction without fatigue allows a continued good field of view plus a more versatile role for the assistants and their greater interest in the operation.

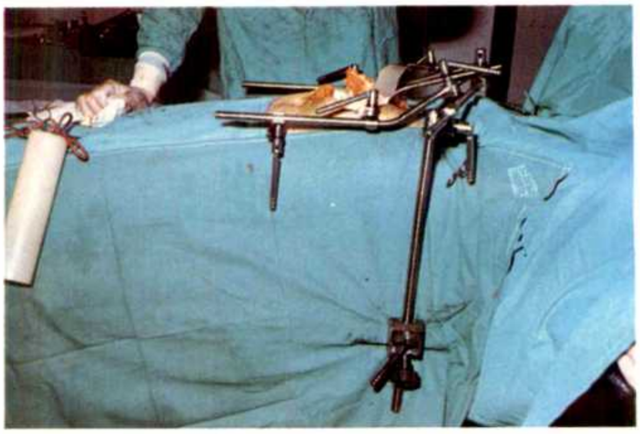

Figure 1 *Retractor and framework*

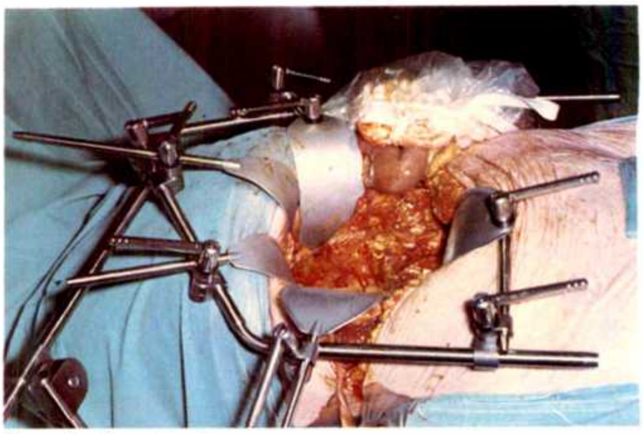

Figure 2 *Operative view*

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Further details of the instrument may be obtained from: CLS Medical Ltd., Alliance House, Roman Ridge Road, Sheffield S9 1GB, UK

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Alteration in colonic epithelial cell DNA associated with intestinal neoplasia: selection of high risk patients

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The proliferative activity of the colonic crypts of patients who are at high risk of developing colonic tumours has been assessed. Cells from the upper parts of the colonic crypts were collected at colonoscopy, and were stained for DNA by the Feulgen technique. Using a microdensitometer the DNA content of the cells was measured and a proliferative index calculated. Patients with single neoplasms had a proliferative index similar to controls although individual patients with hyperplastic mucosa could be identified. Patients with multiple neoplasms had an elevated proliferative index. These results may form the basis of a screening programme for colonic tumours.

Keywords: Colon, DNA, cell kinetics, premalignancy

Changes in the orderly kinetic organization of colonic crypts occur during carcinogenesis. In animal models, there is an increase in crypt cell production rate resulting in crypt hyperplasia[1,2]. Similarly, increases in thymidine labelling indices are seen in those hyperproliferative crypts with an expansion of the proliferative zone due to an upward movement of the cut-off position[3]. Alterations in crypt kinetics are also observed in patients with familial polyposis coli and ulcerative colitis[4–6]. Patient studies are limited owing to the problems of applying cell kinetic techniques to man, since these methods commonly use either tritiated thymidine or metaphase arresting agents. This means that *in vitro* experimentation has to be used for patients rather than direct measurements and so a method of assessing crypt cell proliferation without these limitations would be of some value.

In a normal colonic crypt the cells at the base, the stem cells, are actively dividing although the cell cycle time of the cells is long so few mitotic figures are actually seen in this area[7,8]. As the cells migrate up the crypts into the proliferative zone, cell cycle times reduce and the mitotic index rises[8]. This is the major zone of crypt cell production above which proliferation gradually tails off due to a steady reduction in the proportion of the cycling cells. In the maturation zone cell division is no longer taking place so no mitotic figures or cells in the S or G_2 phases of the cell cycle will be present. The amount of DNA in an individual cell varies with the stage in the cell cycle so proliferative changes in colonic mucosa may be reflected by an alteration in the mean DNA content of the crypt cells. Any mature enterocytes with a hyperdiploid DNA content would indicate abnormal proliferation in the crypts. The Feulgen technique stains DNA stoichiometrically, that is in direct proportion to the amount of DNA present, and the amount of stain in individual cells can be measured by cytophotometry. In this study we have used this technique to measure alterations in cellular DNA in mature enterocytes in patients with large bowel adenomas and carcinomas in order to determine whether proliferative changes associated with carcinogenesis are generalized or locally distributed in the colon.

Patients and methods

Patients

Patients undergoing colonoscopy after either Picolax or Herculaen bowel preparations were divided into four groups: patients with no history of inflammatory bowel disease or neoplastic disease who were found to have either diverticular disease or a completely normal colon acted as controls and were compared to those who were found to have or had previously had (a) a solitary adenoma, (b) a solitary carcinoma or (c) more than one neoplasm, either benign, malignant or both.

At endoscopy colonic cells were obtained by brush cytology from areas of flat, macroscopically normal mucosa throughout the colon. Care was taken not to take samples closer than 10 cm from any neoplasm so as to avoid the transitional mucosa seen adjacent to tumours. Samples were obtained as follows: 45 from 20 control patients; 27 from 19 patients with a solitary adenoma; 35 from 27 patients with a solitary carcinoma and 42 samples from 18 patients with multiple neoplasms were obtained. Of the 18 patients with multiple neoplasms, 8 had adenomas only, 2 had adenocarcinomas only and 8 had adenocarcinomas and adenomas together.

Histochemistry

The cells from each sample were suspended in 5 ml Hanks tissue culture medium containing 10 per cent ethanol and 1 per cent glacial acetic acid. After 24 h the cells were syringed through a 25G needle three times to disaggregate any clumps and were then washed three times in PBS pH7·4. Cytopreparations were made using Shandon cytopsin and these were post-fixed in Carbowax ethanol containing 1 per cent glacial acetic acid and 0·3 per cent polyethylene glycol.

The cytopreparations were dipped briefly in 1 M hydrochloric acid and transferred to 5 M hydrochloric acid at room temperature for 50 min. They were then immersed in the dark, in Schiff's reagent for 1 h and washed in three changes of bisulphite water (2:1 volume:volume, 0·5 per cent potassium metabisulphite to 1 M hydrochloric acid), dehydrated and mounted in DPX.

DNA measurement. Using a Vickers scanning and integrating microdensitometer set at 550 nm with a spot size of 0·5 μm, the amount of stain in 100 cells from each sample having the nuclear shape and morphology of colonic epithelial cells was measured. A mask size of either 10, 15 or 20 μm was used depending on the size of the cells in the sample. The proportion of cells containing a hyperdiploid DNA content was calculated to give a proliferative index (PI) and expressed as a percentage.

Statistics

Since the data were not parametric, a Mann–Whitney *U* test was used to compare the different sets of results.

Results

Proliferative index in patient groups

Controls. The median proliferative indices in the 20 patients without any evidence of colonic neoplasia was 2·0. There were

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Table 1 *Proliferative indices of the different regions of normal colon*

	Median	Range	No. of samples
Ascending	2·0	0–4	9
Transverse	2·0	0–7	8
Descending	3·0	0–6	9
Sigmoid	1·0	0–6	13
Rectum	1·0	0–6	9

small regional variations throughout the colon, the lowest values being found in the rectum, but none of the differences was significant (*Table 2*). The range of values of individual measurements varied from 0 to 7 with 75 per cent of the values being between 0 and 4.

Single tumour. The median value for the proliferative index of flat mucosa obtained for patients with a solitary adenoma was 4·0 which was not significantly different from that obtained for patients with a solitary carcinoma (*Figure 1*). Neither of these values were significantly different from the controls although one patient with a solitary adenoma did have a proliferative index of 14, double the highest value obtained for any of the controls. Four of the patients with a solitary carcinoma had values above the normal range for the controls, and one of these patients had aneuploid cells with a hypertetraploid DNA content.

Multiple tumours. In the 18 patients with multiple tumours, the median value for the proliferative indices was 5·0, significantly greater than the control value ($P<0{\cdot}001$), and the values obtained for the solitary adenomas and carcinomas ($P<0{\cdot}02$) (*Figure 1*). The proliferative indices of these patients was not always consistent throughout the colon. In some patients a single area of colon had a high proliferative index whilst the rest of colon was within the normal range. When the results from all of the patients with multiple neoplasms were divided into the area of colon between 5 and 10 cm from the neoplasm (so as to avoid transitional mucosa) and distal to the neoplasms, the mucosa near to the neoplasms had a proliferative index of 9·0, three times greater than that distal to the neoplasms ($P<0{\cdot}01$) *Figure 2*. The distal mucosa still had a proliferative index of 3·0 which was significantly higher than the control value. There were no significant differences between the proliferative indices obtained for patients with multiple adenomas, multiple carcinomas or a mixture of the two.

Discussion

This study evaluates a novel method of assessing colonic crypt kinetics that does not require the use of enzyme disaggregation, tissue metaphase arresting agents or *in vitro* organ culture and could easily be developed into a routine assay. The proliferative index or the proportion of hyperdiploid cells measures the percentage of cells in S, G_2 and M and therefore will be numerically greater than the thymidine labelling index representing cells only in the S phase.

No significant regional variation in the proliferative index was observed, although in experimental animals both crypt height and crypt cell production rate vary from site to site along the colon[2,8]. Our inability to demonstrate these differences can be explained by the method of obtaining cytological specimens which removes cells predominantly from the upper crypt. These are mature or maturing enterocytes from the functional zone of the crypt where, in normal circumstances, cell division would not be expected. The small numbers of proliferating cells found in the control subjects are cells from the upper part of the proliferative zone that have been removed by the cytology brush.

Main proliferative indices were similar in patients with solitary adenomas and carcinomas and both of these groups did not vary significantly from control subjects. The mean number of hyperdiploid cells in patients with multiple tumours was almost twice that observed in the other three patient groups. The significant increase in proliferative activity would suggest that this cohort of patients differs from other patients both with adenomas and carcinomas. This would be consistent with the clinical behaviour of these sub-groups, all patients with large bowel neoplasia being at increased risk of developing metachronous tumours; however, the risk is more than 20 per cent higher for those with more than one polyp at presentation[9].

Using thymidine labelling techniques with organ cultures of colonic mucosa, increases in the size of the crypt proliferative zone have been recognized in patients with familial polyposis

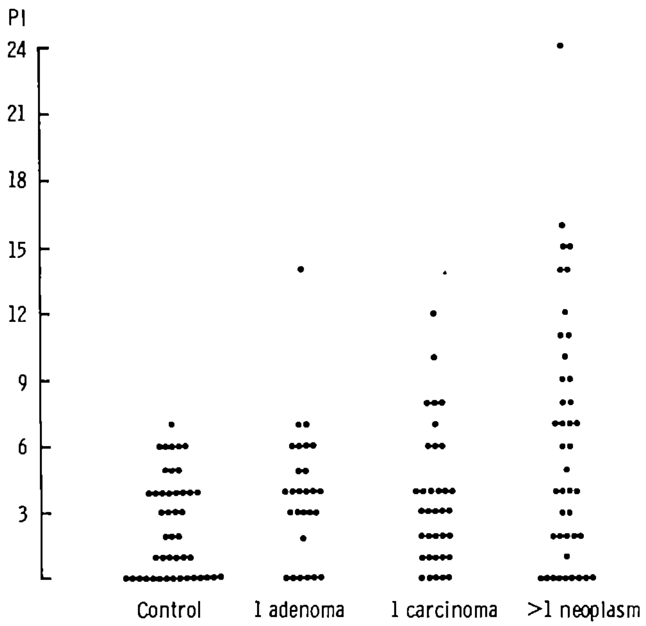

Figure 1 *Scattergram of the proliferative indices (PI) of the four groups of patients. For control compared with >1 neoplasm* $P<0{\cdot}01$

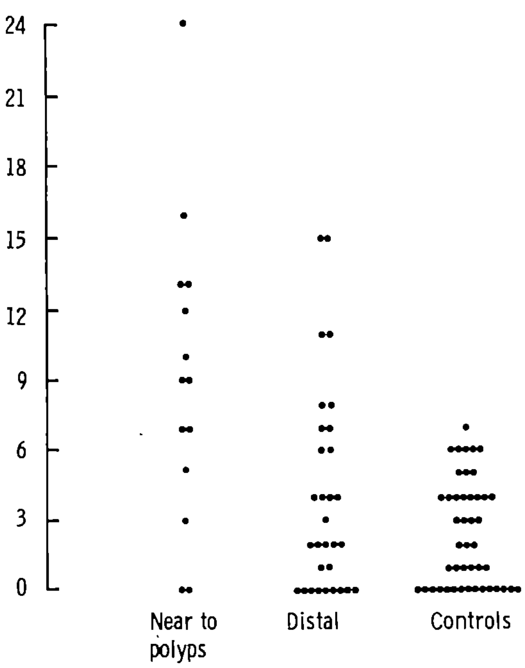

Figure 2 *Scattergram of the proliferative indices of mucosa near to and distal from neoplasms in the patients with multiple neoplasms. For control compared with 'near to polyps'* $P<0{\cdot}01$, *for control compared with 'distal'* $P<0{\cdot}02$

coli and ulcerative colitis[4-6]. By this technique, Lipkin[10] could discriminate between individuals at varying risk of developing colorectal carcinoma. People in the high risk group were observed to have labelled cells in the upper crypt consistent with the present study which observes an increase in hyperdiploid cells in the upper zone of the crypt. However, using the measurement of DNA content has considerable advantages over thymidine labelling. The cells do not have to be maintained in tissue culture and autoradiography is not required both of which may give rise to errors. The added advantage of DNA measurement is that it is relatively quick and could be semi-automated for use in routine screening of patients.

The finding of high proliferative indices will not necessarily improve the management of patients with multiple large bowel tumours, as their risk of developing further tumours is already well established. These patients require careful clinical follow-up by regular colonoscopy. However, it could be useful in selecting those patients with a single polyp or cancer who require a more intensive follow-up. Although the mean proliferative index in these patients is not significantly different to controls some individuals have a level of crypt proliferation activity similar to that of the high risk group. Using methods similar to these it may be possible to select and limit the numbers of patients for screening by colonoscopy which could lead to increase in cost effectiveness and efficiency.

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Surgical workshop

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Removal of retained Foley catheter

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A not uncommon problem is the inability to deflate the balloon of an indwelling urethral catheter. A number of techniques have already been described to bring about deflation of the balloon and removal of the catheter. The most commonly used of these are the passage of the stylet of a ureteric catheter up the balloon inflation channel to deflate or rupture the balloon[1] or ultrasonically guided percutaneous suprapubic puncture of the balloon with a fine needle[2]. Suprapubic puncture with a needle under cystographic X-ray control[3] and passage of a visual urethrotome to puncture the balloon[4] have also been suggested. The injection of various chemicals to dissolve the balloon is no longer acceptable as this does not often work and can cause a chemical cystitis.

A less common, and avoidable, complication presented to us recently when, in an effort to deflate a balloon catheter, the entire catheter was transected and the retained part slipped into the proximal urethra. To remove it a size 26 Storz cystoscope was passed, easily pushing the catheter into the bladder. An oesophageal varices injector was then passed down the ureteric catheterization channel of the instrument. By keeping the bladder virtually empty of fluid, the balloon was held in position by the bladder wall and puncture was successful in spite of the encrustations. The deflated catheter was then easily removed, intact, with a biopsy forceps.

This case illustrates a transurethral method of resolving this problem, which should not be allowed to occur in the first instance, and avoids an open procedure for removal. The important point of technique to be remembered is that of using the non-distended bladder wall to hold the balloon while puncture is attempted.

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Blood transfusion and recurrence of cancer of the colon and rectum

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Clinical and experimental studies indicate that transfusion of allogeneic blood has immunomodulating properties, and that the behaviour of some tumours may be influenced by the immune system of the host. Eighty-seven patients who had undergone 'curative' resection of cancer of the colon or rectum were studied retrospectively to determine whether blood transfusion adversely affected the rate of cancer recurrence. Fifty-three patients (61 per cent) were transfused and 34 were not. The transfused and non-transfused groups were comparable in terms of age, sex, duration of follow-up, mode of presentation, stage of disease and haemoglobin level at discharge from hospital, and differed in admission haemoglobin and distribution of tumour locations (right- or left-sided colonic or rectal tumours). Recurrent malignancy was detected in 36 per cent of transfused patients and 26 per cent of non-transfused patients ($P > 0.1$)*. There was no association between the number of transfusions and recurrence for any tumour site or stage. The incidence of recurrence was significantly higher in those patients who received transfusions during surgery than in those who received transfusion either before or after surgery* ($\chi^2 = 7.01$, $d.f. = 1$, $P < 0.01$) *or no transfusions* ($\chi^2 = 4.23$, $d.f. = 1$, $P < 0.05$)*. The study indicates that factors influencing the need for blood transfusion during operation had a greater bearing on prognosis than receipt of a blood transfusion* per se *and that future prospective studies investigating the association between transfusion and cancer recurrence need to determine accurately the indications for transfusion.*

Keywords: Blood transfusion, carcinoma of the colon, carcinoma of the rectum, cancer recurrence

Recent interest in a possible association between the administration of blood transfusions and recurrence of disease in patients with cancer treated by surgical excision[1–16] has been stimulated largely by transplantation studies which have shown that blood transfusions given to humans before transplantation significantly prolong the survival of renal allografts[17]. Although the exact mechanism of this 'transfusion effect' has not been elucidated fully, evidence strongly suggests that blood transfusions alter the reactivity of the immune system of recipients so that rejection of subsequent allografts, in the presence of chemotherapeutic immunosuppression, is reduced significantly. Clinical and experimental evidence suggests that in some circumstances tumour growth may be influenced by immune responses of the host[18–24], and so the possibility arises that blood transfusions may affect adversely the prognosis of patients with malignant disease by accelerating tumour growth as a result of immunological manipulation.

This study examines the impact of blood transfusion on the outcome of patients treated surgically for cancer of the colon and rectum at a single institution, with the aim of establishing whether or not an association exists between transfusion and recurrence and if so identifying the determinants.

Patients and methods

The case notes of 193 patients treated at the Royal Melbourne Hospital by surgical resection of histologically confirmed cancer of the colon or rectum between 1974 and 1981 inclusive have been reviewed. Information was sought on age, sex, mode of presentation, date of operation, tumour site and stage, degree of tumour differentiation, operative procedure, haemoglobin level before operation and at discharge from hospital, and the clinical status at the most recent attendance at hospital. The transfusion status of each patient was ascertained from blood bank records, in addition to medical records. Patients were considered as having been transfused if they had received whole blood or packed cells at any time before, during or after their operation. No patient received adjuvant chemotherapy or radiotherapy.

Information about the stage of the tumours was obtained from pathology records. Cancers were staged according to the Australian Clinico-Pathological Staging (ACPS) system[25], which is similar to the Dukes' classification[26] except that it includes carcinomas of the colon and operative and clinical assessments of tumour spread are taken into account in addition to histopathological staging. For example, a tumour is classified as ACPS 'D' when there is clinical or microscopic evidence of cancer remaining either locally or at a distance irrespective of the extent of mural penetration or lymph node status. Patients were included in the study if they had undergone a 'curative' resection, which was defined as a resection of the carcinoma together with contiguous tissue including the regional lymph nodes and there was no known tumour remaining either locally or in a distant sites (ACPS A, B or C)[25].

Carcinomas of the colon were classified as either 'right' or 'left' depending on whether the predominant blood supply was from the superior or inferior mesenteric arteries respectively. The duration of follow-up was taken as the interval between the day of operation and the last progress note in the medical record. Patients were excluded from the study if their period of follow-up was less than six months, if their follow-up had been undertaken at another hospital, if the primary tumour had not been resected or if they had synchronous or metachronous colorectal cancers. Eighty-seven patients fulfilled the criteria for inclusion in the study.

Statistical methods

Cumulative percentages of patients surviving without recurrence calculated by the life table method of Cutler and Ederer[27]. The χ^2 analysis was used to test the significance of differences between

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Table 1 *Details of transfused and non-transfused patients*

	Transfused (%)	Non-transfused (%)
Number	53 (61)	34 (39)
Age (years) (mean ± s.d.)	66·2 ± 11·5	66·5 ± 11·4
Male/female	0·76	0·88
Presentation		
Elective	45 (85)	31 (91)
Emergency	8 (15)	3 (9)
Duration of follow-up (months) (median and range)	52 7–103	53 8–94
Site		
Right*	27 (51)	10 (29)
Left	10 (19)	17 (50)
Rectum†	16 (30)	7 (21)
Stage		
A	2 (4)	3 (9)
B	31 (58)	21 (62)
C	20 (38)	10 (29)
Haemoglobin (g/dl) (median ± s.d.)		
Admission‡	10·2 ± 2·0	14·1 ± 1·4
Discharge	12·1 ± 1·3	12·2 ± 1·4
Recurrent disease	19/53 (36)	9/34 (26)

*Right *versus* left: $\chi^2=8{\cdot}26$, d.f. = 1, $P<0{\cdot}01$
†Rectum *versus* left: $\chi^2=5{\cdot}26$, d.f. = 1, $P<0{\cdot}05$
‡Transfused *versus* non-transfused: $P<0{\cdot}001$, Student's *t* test

proportions except for the analysis of disease free survival when the method of Peto *et al.*[28] was used. The Student's *t* test was used to test the significance of differences between the means of haemoglobin levels of transfused and non-transfused groups.

Results

Fifty patients were transfused within two weeks of operation and another three had been transfused previously; 34 patients (39 per cent) were not transfused (*Table 1*). There was no statistically significant difference between the transfused and non-transfused groups in terms of sex, age, duration of follow-up or stage of disease. Although a higher proportion of patients presenting as emergencies were transfused in comparison with patients presenting electively, the difference was not statistically significant (8 of 11 (73 per cent) *versus* 45 of 76 (59 per cent) = $\chi^2=0{\cdot}73$, d.f. = 1, $P>0{\cdot}1$). A significantly lower proportion of patients with left-sided colonic tumours were transfused than those with right-sided or rectal tumours (χ^2 test: $P<0{\cdot}01$ and $P<0{\cdot}05$ respectively). Pre-operative haemoglobin levels were significantly lower in transfused than in non-transfused patients (10·2 ± 2·0 g/dl *versus* 14·1 ± 1·4 g/dl; Student's *t* test, $P<0{\cdot}001$), whereas haemoglobin levels before discharge from hospital did not differ significantly.

Thirty-six of the thirty-seven patients with carcinoma of the right colon were treated by right hemicolectomy and the remaining patient was treated by subtotal colectomy with an ileorectal anastomosis. Two of the twenty-seven patients with left-sided colonic lesions were treated by extended right hemicolectomy and the remaining 25 underwent left hemicolectomy or sigmoid colectomy. Of 23 patients with rectal cancer 12 underwent anterior resection (AR) with handsewn anastomoses and 11 underwent abdominoperineal resection (APR). Although there was no significant difference between the distribution of the three ACP stages between lesions treated by AR or APR, all 11 patients who underwent APR were transfused while only 5 of 12 patients treated by AR were transfused.

Recurrent disease was diagnosed in 28 patients (32 per cent), 19 of 53 (36 per cent) who had been transfused and 9 of 34 (26 per cent) who had not ($\chi^2=0{\cdot}83$, d.f. = 1, $P>0{\cdot}1$). The cumulative percentages of patients surviving without recurrence are shown in *Figure 1*. Although there is no statistically significant difference between the disease-free intervals of the two groups, non-transfused patients had a slight but consistent disease-free advantage (log rank $\chi^2=0{\cdot}86$, d.f. = 1, $P>0{\cdot}1$). Non-transfused patients with carcinoma of the left colon or rectum had a lower incidence of recurrence than their transfused counterparts (left colon: 24 per cent *versus* 60 per cent; rectum: 29 per cent *versus* 63 per cent), although these differences did not reach statistical significance. No statistically significant association was found between transfusion status and cancer recurrence for any stage of disease at any tumour location, except in patients with ACPS 'C' carcinomas of the right colon—all three non-transfused patients suffered recurrent disease (*Table 2*). Of the 12 patients undergoing AR for rectal cancer, recurrence occurred in 4 of 5 (80 per cent) transfused patients and in 2 of 7 (29 per cent) non-transfused ($\chi^2=3{\cdot}08$, d.f. = 1, $P>0{\cdot}05$).

The median number of units of transfused blood in patients with and without recurrent disease was two (range 1–7) and three units (range 1–25) respectively. No association was found between the number of transfusions and recurrence for any tumour site or stage. Tumour recurrence in relation to the timing of transfusion is shown in *Table 3*. There was a significantly higher recurrence rate in patients given blood during the surgical procedure, with or without other transfusions, than in patients given blood only before or after surgery: 15 of 29 (52 per cent) compared with 4 of 24 (17 per cent), ($\chi^2=7{\cdot}01$, d.f. = 1, $P<0{\cdot}01$). Similarly, a significantly greater number of patients transfused only during their operation ('peroperatively transfused') developed recurrence than those who received blood only before or after surgery: 12 of 24 (50 per cent) compared with 4 of 21 (19 per cent), ($\chi^2=4{\cdot}68$, d.f. = 1, $P<0{\cdot}02$).

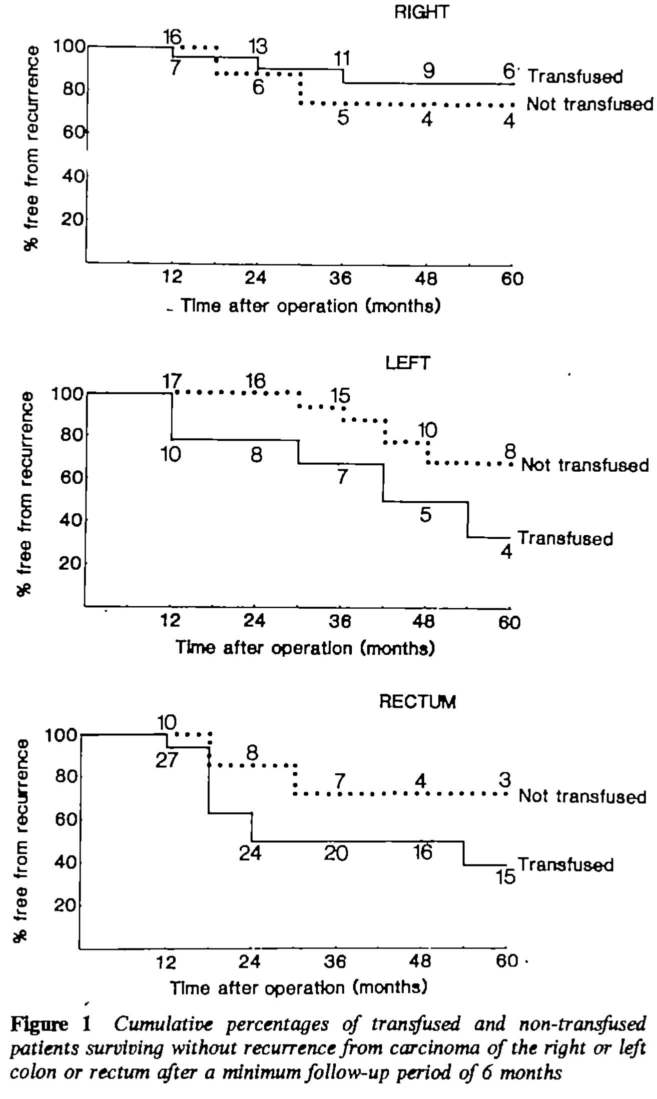

Figure 1 *Cumulative percentages of transfused and non-transfused patients surviving without recurrence from carcinoma of the right or left colon or rectum after a minimum follow-up period of 6 months*

Table 2 *Distribution of recurrent malignancy by tumour location and stage in transfused (T) and non-transfused (NT) patients, expressed as the number of patients with recurrence/number at risk (%)*

	Tumour location					
	Right		Left		Rectum	
Stage	T	NT	T	NT	T	NT
A	0/1	0/2	0	0	0/1	0/1
B	2/18 (11)	0/5	3/5 (60)	2/12 (17)	4/8 (50)	1/4 (25)
C*	1/8 (13)	3/3 (100)	3/5 (60)	2/5 (40)	6/7 (86)	1/2 (50)
All	3/27 (11)	3/10 (30)	6/10 (60)	4/17 (24)	10/16 (63)	2/7 (29)

*Stage C, right-sided colonic tumours, T *versus* NT: $\chi^2 = 7{\cdot}21$, d.f. = 1, $P < 0{\cdot}01$

Table 3 *Relationship between the timing of transfusion and the proportions of patients with recurrent malignancy for each tumour location, expressed as the number with recurrence/number at risk (%)*

	Tumour location			
Transfusion	Right	Left	Rectum	All
None	3/10 (30)	4/17 (24)	2/7 (29)	9/34 (26)*
Per-operative + other	2/11 (18)	4/5 (80)	9/13 (69)	15/29 (52)
Pre- or postoperative only	1/16 (6)	2/5 (40)	1/3 (33)	4/24 (16)†

*Peroperative *versus* none (all patients): $\chi^2 = 4{\cdot}23$, d.f. = 1, $P < 0{\cdot}05$
†Peroperative *versus* pre-operative/postoperative (all patients): $\chi^2 = 7{\cdot}01$, d.f. = 1, $P < 0{\cdot}01$
'Peroperative' = transfusion during surgery
'Pre- or postoperative' = transfusion before or after surgery

The proportion of rectal cancers was significantly greater in the group transfused during surgery than in the other transfusion groups: 13 of 29 patients transfused during surgery had rectal tumours whereas only 3 of 24 patients transfused at some other time had rectal neoplasms ($\chi^2 = 6{\cdot}51$, d.f. = 1, $P < 0{\cdot}02$). This preponderance of rectal lesions does not explain the poorer prognosis of the peroperatively transfused group as both left-sided colonic and rectal cancer patients who were transfused during surgery had higher recurrence rates than patients with tumours in these same sites but who were given only pre- or postoperative transfusions or none at all, although the difference did not always reach statistical significance (*Table 3*).

Discussion

Although the relationship between tumour behaviour and the host's immune system is complex, some human and animal tumours stimulate specific tumour-directed immune responses and may be influenced by the immune status of the host. Cutaneous delayed hypersensitivity reactions have been observed against autologous and allogeneic tumour cells[29] and histological studies have shown infiltration of tumours by immunologically active lymphoid cells of host origin[30]. Deterioration of immune parameters has been observed in some patients shortly before recurrent malignancy has become clinically apparent, although it is uncertain whether such changes are a cause or an effect of advancing disease[21–23]. Also, long-term immunosuppresssion of allograft recipients is associated with a higher incidence of many malignant diseases than is observed in the general population[24]. Therefore, it is possible that a procedure (including blood transfusion) which impairs immune responsiveness and which is not directly cytoreductive may alter the balance of host–tumour interaction in favour of accelerated tumour growth.

Transfusion of blood has significant effects of the recipient's immune system. Allogeneic blood induces antigen specific and non-specific suppressor T lymphocytes[31,32], increases suppressor cell activity[33] and reduces natural killer cell activity[34]. Damaged erythrocytes in transfused blood may impair mononuclear phagocytic cell function[35] and the finding of a diminished mixed lymphocyte reaction after transfusion has been attributed to phagocytic cell depletion[36]. Immune complexes have been detected in plasma after transfusion[37]. The non-specific lymphocyte suppressive activity of plasma is increased in uraemic dialysis patients after transfusion[38], largely as a result of changes in the conformation and biological behaviour of the plasma protease inhibitor α_2 macroglobulin and the appearance in plasma of a small molecular weight peptide[39]. Allogeneic transfusion has been shown to increase the number of circulating IgG-, IgM- and IgA- secreting cells in immunologically normal subjects[40], as well as inducing a variety of antibodies including non-cytotoxic anti-Fc receptor antibodies[41], donor specific lymphocytotoxins[42] and anti-idiotypic antibodies[43]. Although the relative importance of these observations is uncertain, the overall immunological consequence of allogeneic blood transfusion appears to be a state of diminished immune reactivity within the recipient, a concept supported by clinical and experimental transplantation studies[17]. However, transfusion in clinical organ transplantation does not parallel the use of blood in cancer patients: potential renal transplant recipients are transfused before receiving the antigenic stimulus of the allograft and long-term immunosuppression, whereas transfused cancer patients receive blood at some time (presumably many months) after the development of a tumour which may be already associated with immunological impairment[44]. Therefore, the conclusions from transplantation studies may not be applicable to patients with cancer.

Since 1982 ten published reports have claimed statistically significant associations between blood transfusion given at the time of definitive surgery and early recurrence of malignant disease of soft tissues[14], breast[2,13], lung[5,16] and the colon and rectum[1,3,4,11,12]. Rosenberg *et al.* reviewed 156 patients who underwent excision of high grade soft tissue sarcomas of the extremities and found a highly significant difference in the 5-year overall and disease-free survival rates between transfused and non-transfused groups[14]. However, the 'transfusion effect' was present only in those patients who had received four or more units of blood and only in those who were randomized to receive adjuvant chemotherapy. Rosenberg *et al.* found that perioperative transfusion was strongly associated with tumour size and the extent of resection and was a significant independent prognostic variable[14], suggesting that the indication for transfusion may have had a bearing on prognosis. Blumberg reviewed 197 patients with 'colorectal' cancer and found that blood transfusion was more closely associated with cancer recurrence than any other prognostic factor including Dukes' stage[11]. However, the patients in the study were highly selected and several important prognostic factors, including tumour site and operative procedure, were not analysed. Tartter *et al.* found that the cumulative disease-free survival of 169 patients treated by mastectomy and axillary dissection for stage I, II or III breast cancer was significantly reduced in transfused patients[13]. Admission haemoglobin levels were lower and operative blood loss was higher in patients who were transfused, suggesting that pre-existing bone marrow suppression or the extent of the surgical procedure was greater in these patients. In the studies by Tartter *et al.*[13] and Blumberg *et al.*[11] significantly higher proportions of transfused than non-transfused patients received adjuvant chemotherapy or radiotherapy, and so the transfused groups may have had more aggressive and extensive disease, or a higher proportion of patients in whom it was believed that surgical resection was not curative.

Two reports have claimed that perioperative blood transfusion reduced the survival of patients undergoing resections for carcinoma of the lung[5,16]. However, in the study by Tartter *et al.*[5] there was no statistically significant difference in survival between transfused and non-transfused groups after correction for the extent of the surgical resection. In the study by Hyman *et al.* of 155 patients undergoing curative or palliative resections of stage I, II or III carcinomas of the lung the difference in five year survival rates between transfused and non-transfused groups was only 'marginally significant ($P = 0{\cdot}09$)'[16].

These and other studies[1–5,11–14,16] fail to provide convincing evidence for the existence of an association between blood transfusion and cancer recurrence. All are retrospective and most fail to identify important prognostic variables. In none of the studies, including our own, was it possible to define accurately the indications for transfusion. If blood was transfused according to clinical need the transfused and non-transfused groups were not comparable as they may have differed in such factors as pre-existing suppression of the haemopoietic system, extent of the tumour (even correcting for tumour stage), extent of surgical resection, operative blood loss, and the patients' ability to withstand blood loss, as well as their general health. Such factors may influence the outcome of surgery for malignant disease and are of great importance when deciding to prescribe blood, and yet they cannot be measured easily by conventional means. Blood transfusion could be an index of these and other important prognostic factors.

Few studies have considered the importance of the timing of transfusion in relation to cancer recurrence. Burrows and Tartter found identical 5-year cumulative recurrence-free survival rates among patients who were transfused either before, during or after resection of colonic and rectal cancers[1,4]. The present study found that peroperative transfusion alone or in combination with pre- or postoperative transfusions was associated with a statistically significant increase of recurrence in comparison with pre- or postoperative transfusions alone. Thus, recurrence was associated with the need for transfusion during the surgical procedure, an observation which suggests that recurrence was related more to operative factors than to transfusion *per se.* Although several studies attempted to take account of the influence of operative factors upon recurrence by assessing estimated operative blood loss[5,13], extent of resection[4,5] and duration of operation[5,11], such parameters do not measure operative difficulty, fixation of the tumour to adjacent structures, or operative spillage and dissemination of tumour cells, all of which have a bearing on prognosis.

Six studies have failed to find a statistically significant association between blood transfusion and early recurrence in patients treated for carcinoma of the breast[6,7], colon and rectum[8–10] and kidney[15]. Interestingly, in most reports transfused patients had a slightly worse prognosis than non-transfused. These studies are retrospective, involve relatively few patients and are open to the same criticisms as cited previously.

Two authors have reported briefly on the incidence of non-cutaneous malignancy in transfused and non-transfused recipients of successful renal allografts. Opelz found no increase in incidence of tumours arising *de novo* in transfused patients on the Denver Kidney Transplant – Tumour Register[45]. Birkeland reported a Scandanavian series of 531 patients in whom there was a highly statistically significant increase in tumour incidence amongst transfused allograft recipients[46]. The significance of these observations is impossible to determine as many variables were not reported.

The present study of a small number of patients found that the need to transfuse during surgical excision of cancer of the colon or rectum was associated with a higher recurrence rate than if transfusions were given before or after surgery, and therefore suggests that operative factors such as the extent of the tumour and difficulty of resection are more important prognostic factors than receipt of a blood transfusion *per se.* Retrospective studies by their nature are unable to identify many of the variables which influence the prognosis of cancer patients or the decision to transfuse them, and so carefully controlled prospective studies are required[8]. Such studies present enormous problems in their design and conduct, and it is clearly unethical to randomize patients either not to receive a transfusion which is indicated clinically or to receive a treatment which may not be required and in some respects could be detrimental. However, studies could be undertaken using 'washed' packed red blood cells, synthetic blood substitutes or pre-donated autologous transfusions from some suitable non-anaemic patients, and could include the few patients who refuse transfusions. Even if an association between cancer recurrence and blood transfusions was confirmed by prospective studies it may not be necessary to implicate immunological mechanisms. Blood transfusion could be simply identifying tumours with an intrinsically poor prognosis – for example, an 'aggressive' malignancy might be associated with tumour ulceration or perineoplastic inflammation which, in colorectal cancer, might lead to transfusion before or during operation respectively. Interestingly, ulceration is a poor prognostic feature of malignant melanoma[47], the surgical treatment of which infrequently requires transfusion.

At present there is little evidence to support the existence of a direct causal relationship between blood transfusion and early recurrence of surgically treated cancer. Thus, we are unable to extrapolate justifiably the results of clinical and experimental studies of blood transfusion in organ transplantation to patients undergoing surgery for malignant disease, and we believe that it is unreasonable deliberately to avoid transfusing cancer patients in the presence of clinical need.

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Late results of mucosal proctectomy and colo-anal sleeve anastomosis for chronic irradiation rectal injury

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Ten patients with severe chronic irradiation injury to the rectum were treated by mucosal proctectomy and colo-anal sleeve anastomosis. The indications were: recurrent rectal bleeding (five), stricture (three), fistula (one) and intractable pain (one). Overall follow-up has ranged from 8 to 77 months (mean 40 months). In the present survivors (n = 7) *the follow-up ranges from 18 to 77 months (mean 52 months). Six patients have been followed up for more than 3 years and four for more than 5 years. There was no operative mortality. Three anastomotic strictures occurred but the protecting stoma could be closed in all but one patient. Continence was acceptable although urgency and frequency of defaecation were troublesome symptoms. The operation is recommended for life-threatening, haemorrhagic chronic irradiation injury to the rectum.*

Keywords: Irradiation rectal injury, haemorrhagic proctitis, colo-anal sleeve anastomosis, anorectal function

Radiotherapy makes an important contribution to the treatment of malignant disease arising in the pelvis. Some irradiation of adjacent healthy tissue inevitably occurs, the rectum being most commonly involved[1–6]. The symptomatic disturbances from chronic irradiation rectal injury are distressing[1–7]; the organic complications such as haemorrhage and perforation can be life-threatening and may necessitate urgent surgical intervention[2–6]. Surgical excision of the irradiation-injured rectum may be extremely hazardous and its risks have been repeatedly emphasized. Anterior resection, Hartmann's procedure and abdominoperineal excision of the rectum are all associated with an unacceptably high incidence of anastomotic dehiscence, poor tissue healing and chronic pelvic sepsis[2,3,5]. The late Sir Alan Parks described a technique of anastomosis between healthy proximal colon and the anal canal within a sleeve of rectal muscle denuded of mucosa[8]. This procedure avoids extensive pelvic dissection and preserves the anal sphincter musculature and its innervation. It has been applied successfully to the treatment of a number of different conditions including irradiation-induced rectovaginal fistula[3,9]. However, the long-term results of the operation when performed for more extensive irradiation rectal injury have received little attention. We describe the clinical progress and long-term results in ten patients treated by this method for severe chronic irradiation injury to the rectum. Based on previous experience[6,7] and these results, a protocol is suggested for the management of delayed irradiation injury to the rectum requiring surgical intervention.

Patients and methods

Table 1 lists details of the ten patients treated between 1979 and 1985. Their mean age was 65 years; eight patients were over the age of 60 years. Before radiotherapy two patients had a Hartmann's procedure for complications of diverticular disease. Seven patients had been treated for carcinoma of the urinary bladder. Five of these had received small field (10 x 10 cm) external beam radiotherapy (5500 cGy in 20 treatments over 4 weeks), and two had received neutron therapy using the small-field (11 x 11 cm) technique (mean dose to the bladder 300 cGy for ten treatments over 4 weeks; mean dose to the whole pelvis 1300 cGy for ten treatments over 4 weeks). The three patients with cervical cancer had received whole pelvis, external beam radiotherapy supplemented by a single caesium implant (cumulative dosage of 9500 cGy to the vaginal vault, equivalent to 7500 cGy to point A).

Five patients had experienced recurrent life-threatening rectal bleeding requiring several hospital admissions and repeated blood transfusions (*Figure 1*). All the irradiation patients had undergone courses of intensive medical therapy in an attempt to control their rectal symptoms. The patients were assessed jointly by a senior surgeon and radiation oncologist to exclude recurrent malignant disease; radiological investigations were also performed to assess the site, extent and severity of damaged bowel. Before they could be considered for rectal excision, six patients required a preliminary laparotomy and transverse colostomy to defunction severely diseased distal bowel. At this procedure a full assessment of the abdomen and pelvis was also made to exclude recurrent malignancy.

Anal sphincter function was assessed clinically and manometrically in most of the patients[10].

Operative technique

The bowel was prepared as for a major colonic resection[11]. In those patients with a loop colostomy the distal colon was additionally cleansed by saline washouts on the day before operation. Prophylactic antibiotics were used and continued for 5 days postoperatively. With the patient in the modified Trendelenburg lithotomy position a careful laparotomy was performed, to assess the extent of inflammation and confirm the absence of metastatic disease. Excision of the rectum was then performed to mid-rectal level, sparing approximately 6–7 cm of distal rectum. The site of section proximally was determined by the extent of the macroscopic irradiation damage and the presence and extent of diverticular disease. Sufficient healthy proximal colon was mobilized to reach the anal canal, ensuring adequate vascularity.

The anastomosis was performed peranally[12] using a Park's self-retaining retractor to expose the anorectal mucosa. After infiltration of the submucosa with saline containing adrenaline (1:300 000) the rectal mucosa was excised in strips from the underlying circular muscle, preserving a 1 cm cuff of mucosa above the dentate line. The proximal colon was then pulled through the denuded rectal muscle tube to lie without tension in the sacral concavity. The anastomosis was fashioned approximately 1 cm above the dentate line. Using interrupted polyglycolic acid sutures, full-thickness bites were taken of both the colon and the upper part of the internal anal sphincter (*Figure 2*).

A soft rubber drain was placed in the pre-sacral space behind the transposed colon. In the absence of a proximal stoma, a loop transverse colostomy[13] was fashioned in the right upper quadrant; one patient did not have a protecting stoma. Stomas were closed when the anastomosis was clinically healed and any stenosis present had been dilated. Tests of anorectal continence were performed in several patients.

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Table 1 *Clinical details of ten irradiated patients showing treatment and complications*

No.	Age	Sex	Carcinoma	Treatment	Onset of symptoms following radiotherapy (months)	Complications	Time from presentation to resection (months)	Duration of treatment (months)	Time to closure of colostomy (weeks)
1	80	F	Bladder	XRT	12	Proctitis Stricture (8 cm) Haemorrhage	17	16 (Medical) 1 (Loop colostomy)	10
2	67	F	Bladder	XRT	9	Proctitis Stricture (11 cm)	21	8 (Medical) 13 (Loop colostomy)	7
3	72	F	Bladder	XRT	15	Proctitis Haemorrhage	24	24 (Medical)	6
4	70	M	Bladder	Neutron XRT	9	Proctitis Stricture Obstruction	4	1 (Medical) 2 (Loop colostomy)	10
5	61	M	Bladder	Neutron XRT	6	Proctitis Stricture (10 cm) Haemorrhage	6	2 (Medical) 4 (Loop colostomy)	—
6	68	F	Cervix	Hartmann's XRT	6	Proctitis Haemorrhage	2	2 (Medical)	8
7	57	F	Cervix	Hartmann's XRT	7	Proctitis Pain	2	2 (Medical)	11
8	67	F	Bladder	XRT	6	Proctitis Haemorrhage	12	9 (Medical) 3 (Loop colostomy)	30
9	69	F	Bladder	XRT	1	Proctitis Stricture (15 cm) Ileitis	15	15 (Medical)	No colostomy
10	35	F	Cervix	XRT	2	Fistula (5 cm) Proctitis Stricture (2 cm)	17	10 (Medical) 7 (Loop colostomy)	7

XRT, X-ray therapy

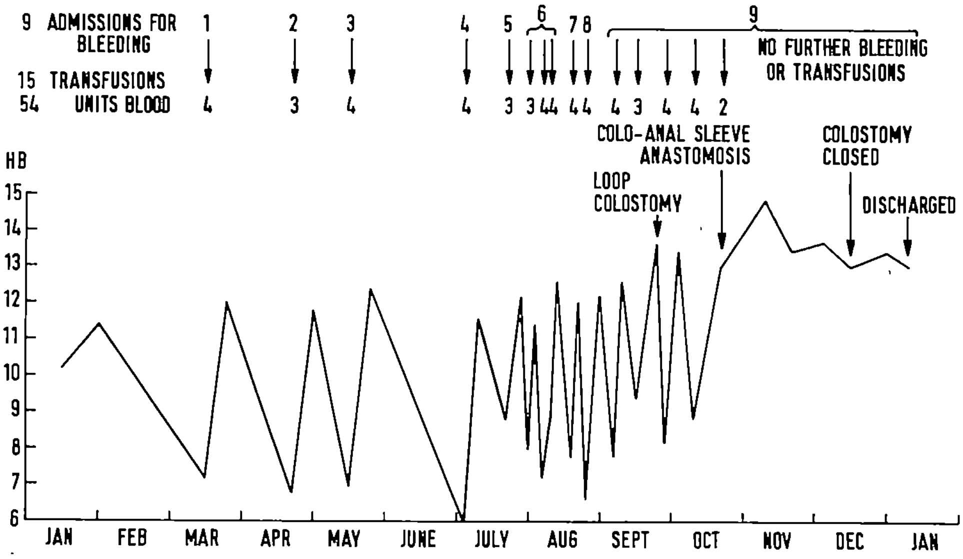

Figure 1 *Graph showing haemoglobin level, emergency admissions and blood transfusions in one of the patients with severe haemorrhagic irradiation proctitis during 1979. Recurrent haemorrhage continued despite a proximal colostomy*

Follow-up and assessment

Follow-up has ranged from from 8 to 77 months ($n = 10$, mean 40 months) in the whole group and from 18 to 77 months in the present survivors ($n = 7$, mean 52 months). Six patients have been followed up for more than 3 years, and four patients for more than 5 years.

At each clinic visit continence and bowel function were assessed objectively according to a predefined protocol. Continence was graded A (fully continent), B (continent for solid stool only), or C (incontinent for both solid and liquid stool). Continence for flatus was not taken into consideration. Frequency and urgency of defaecation were also noted, and discrimination between stool and flatus was assessed.

Results

Complications

There was no operative mortality. The early complications (three perianastomotic abscesses, three anastomotic strictures, one stomal haemorrhage) were managed successfully by conservative measures. The late complications are of more interest. In the irradiation group, there were three anastomotic strictures, two in neutron irradiated patients. All were treated by repeated dilatation but in one patient (patient 5, *Table 1*) the protecting colostomy could not be closed owing to the severity of the stricture. One patient (patient 1, *Table 1*) developed a stricture 5 years postoperatively and required re-establishment of a colostomy. A second patient (patient 10, *Table 1*) developed a vesicovaginal fistula 3 months after closure of the colostomy and is awaiting repair.

Stomas

The mean time to closure of the protecting stoma was 11 weeks

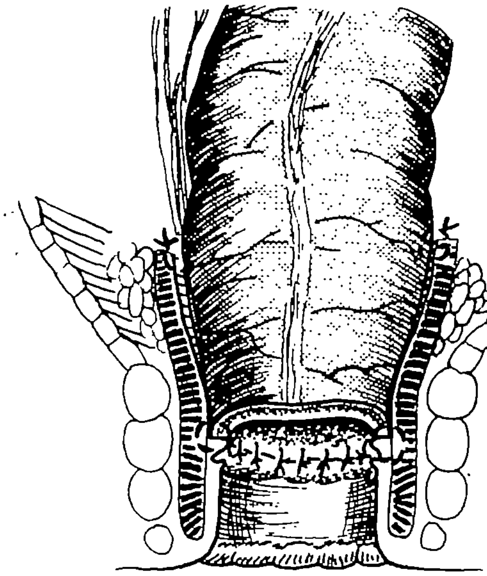

Figure 2 *Diagrammatic representation of colo-anal sleeve anastomosis (modified from Parks AG). Note the preservation of the anal sphincters and pelvic floor musculature. Reproduced from Surgical Techniques Illustrated 1977; 2: 63–70 with permission of Little Brown Company*

(range 6–30 weeks). There are two permanent colostomies to date.

Anorectal function

Five patients had continence Grade A, two patients Grade B and one patient Grade C. Urgency and frequency of defaecation by day and night have been the most troublesome symptoms, despite medical measures. One patient (Grade C) wears an incontinence pad permanently. Four out of eight patients admitted poor anorectal discrimination between flatus and faeces.

Late deaths

There have been three deaths. None was related to the primary disease or operation. Two male patients who had received neutron therapy for bladder carcinoma died 15 and 8 months after operation from myocardial infarction and massive pulmonary thrombo-embolism. A third patient who had been treated successfully for cervical carcinoma died 22 months after operation from a brain stem haemorrhage.

Discussion

Colo-anal sleeve anastomosis[8,11] has been used for a variety of rectal conditions including large rectal haemangiomas, extensive villous adenomas of the rectum, rectovaginal fistulae, low rectal carcinomas and severe irradiation injury to the rectum[9,14–16]. Because a sleeved anastomosis avoids the hazards of deep dissection in an inflamed and fibrosed pelvis, it has been regarded as an advance in the surgical management of the irradiation injured rectum[3,9]. This is exemplified by the results in our patients with recurrent severe rectal haemorrhage which only ceased following operation (*Table 1*); in these patients the procedure was life-saving. Preservation of the anal sphincter is an added attraction and important consideration as many of the patients are elderly. It can be important in such patients to avoid a perineal wound and permanent colostomy associated with complete rectal excision. Our experience with this operation over a 6 year period with careful follow-up has permitted an accurate assessment of its immediate and long-term functional results. Previous clinical and pathological studies have distinguished two types of irradiation intestinal injury. Early symptoms occur during treatment and are due to a reversible direct injury to the intestinal mucosa. Up to 75 per cent of patients may be affected, usually by transient mild proctocolitis which subsides following cessation of radiotherapy. In contrast, delayed abnormalities appear after a latent interval of 6 months to 30 years and are due to progressive ischaemia from irradiation induced changes affecting the intestinal vasculature[17]. Only 2–5 per cent of patients are affected but the pathological changes are severe and irreversible. Conservative treatment is of little benefit, although every effort was made in our patients to relieve symptoms by this approach. Although a proximal colostomy was beneficial in the presence of stricture or fistula, it did not relieve tenesmus, discharge and haemorrhagic complications.

Despite the advanced age of the patients, no operative mortality was sustained. The early postoperative complications were as expected with any low pelvic anastomosis and did not present problems in management. Two of the three chronic anastomotic strictures occurred in patients who had received neutron therapy and developed particularly severe irradiation injuries, suggesting that progressive irradiation-induced ischaemia contributed to their aetiology[17]. Nevertheless, one of these patients managed successfully without a colostomy for 5 years. A similar factor was probably also responsible for the late development of a vesicovaginal fistula in one patient.

Continence has been acceptable overall. The most troublesome and distressing symptoms have been urgency and frequency of defaecation by day and night. These symptoms often occur after low anterior resection of the rectum in the early postoperative period but in most patients tend to resolve later as rectal capacity and compliance improve[18]. This symptomatic improvement did not occur with the irradiation patients. There is evidence that rectal compliance is severely and permanently compromised in irradiation injury to the rectum[7,10], this may be partly due to myenteric plexus injury[10]. Minor degrees of postoperative 'cuff' sepsis may also be contributory[15]. Internal sphincter dysfunction is also present[19] and may be exacerbated by stretching of this muscle during the peranal anastomosis[20]. All these factors may have contributed to the functional disturbances observed in these patients[10]. It is conceivable that rectal function may be less compromised by leaving a shorter 'cuff' and performing a routine posterior proctotomy, especially in the presence of rectal narrowing. Furthermore, there is evidence that balloon dilatation of the rectum at a later time can improve its function[21]. A 1 cm cuff of mucosa was left above the dentate line to retain anorectal discriminatory function and therefore help maintain continence[22]. However some patients admitted to very poor discrimination between flatus and faeces. This may be due to accompanying abnormalities of internal sphincter function and loss of rectal compliance[10]. There is also evidence that transposition of the transverse colon to the pelvis can itself result in motility disturbances[23].

Figure 3 illustrates a protocol for the surgical management of the severely irradiation-injured rectum. It is important that recurrence of malignancy be excluded before a colo-anal procedure is considered. This should be done by an examination under anaesthesia pre-operatively in conjunction with the radiation oncologist and at laparotomy. A proximal loop colostomy before colo-anal anastomosis is useful in the presence of distal obstruction or fistula but is unlikely to influence the haemorrhagic complications. It is, however recommended as a protecting stoma at the time of the definitive operation. Clinical and laboratory tests of anorectal function are useful before closure of the protecting stoma. Severe loss of rectal compliance and/or anal sphincter dysfunction would be contra-indications to colostomy closure. This long-term study suggests that colo-anal sleeve anastomosis is an acceptable and preferred operation for the surgical treatment of the severely irradiation-injured rectum, especially in the haemorrhagic, life-threatening situation.

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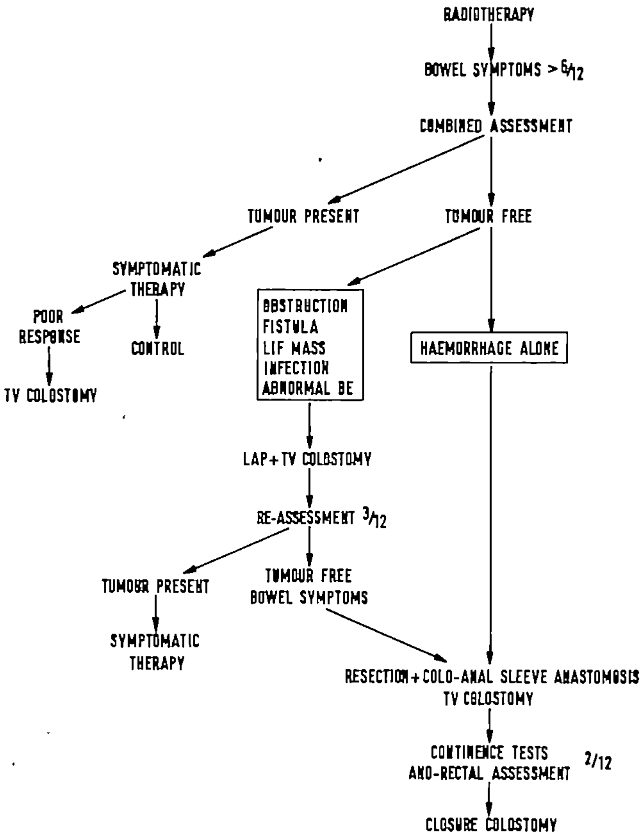

Figure 3 *Suggested protocol for the surgical management of chronic irradiation injury to the rectum. Life-threatening haemorrhage may necessitate primary excision and colo-anal sleeve anastomosis. Other complications may require laparotomy and transverse colostomy. (Abbreviations: BE, barium enema; LIF, left iliac fossa; LAP, laparotomy; TV, transverse; 2/12, 3/12 and 6/12, 2, 3 and 6 months)*

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Duodenum-preserving total pancreatectomy for end stage chronic pancreatitis

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The classical Whipple procedure for chronic pancreatitis has been associated with significant long term postoperative morbidity. The pylorus-preserving procedure of Longmire has reduced but not eliminated the long-term morbidity. Preservation of the whole duodenum with total pancreatectomy has been introduced for the treatment of patients with end-stage chronic pancreatitis after favourable experience with this procedure in infants for nesidioblastosis. Fourteen patients with chronic pancreatitis have had a total pancreatectomy with preservation of the duodenum and the bile duct. All patients are still alive (median follow-up 9·5 months) and none suffered major complications in the perioperative period. One patient developed a biliary stricture at 3 months, requiring biliary reconstruction. Six of the patients have returned to full-time work; nine require no analgesia. All patients require pancreatic enzyme replacement, and all patients have gained weight postoperatively. Diabetic control is satisfactory with a twice daily insulin regime. Duodenum-preserving total pancreatectomy is feasible in the adult without mortality or high morbidity; early experience suggests that preserving the duodenum improves gastrointestinal function with easier control of the diabetes.

Keywords: Pancreatitis, pancreatectomy

Pancreatic resection has been used in the management of chronic pancreatitis with good results[1,2]. The one stage pancreatoduodenectomy described by Whipple in 1946 was performed for both periampullary carcinoma and for chronic inflammation causing intractable pain. At that time, he argued that resection of the duodenum was necessary to achieve clearance of the tumour and because 'complete removal of the head of the pancreas so compromises the blood supply to the duodenum as to favour necrosis and fistula formation'[3].

Warren showed that the original Whipple procedure in which the stomach was transected just proximal to the pylorus was associated with a 17 per cent incidence of anastomotic ulceration and that, by incorporating a more radical gastrectomy with or without vagotomy, the jejunal ulceration rate was reduced to 7·5 per cent[4]. Unfortunately, partial gastrectomy is associated with significant morbidity in terms of dyspepsia, diarrhoea and the dumping syndrome[5].

Traverso and Longmire argued that when pancreatoduodenectomy is performed for benign disease resection of the stomach and the pylorus is inappropriate[6]. Hence, they introduced the pylorus-preserving pancreatoduodenectomy to reduce the nutritional disability which follows the Whipple procedure and preserve normal gastric emptying. However, pylorus-preserving pancreatoduodenectomy involves duodenal resection with loss of the alkaline duodenal secretions which may prevent jejunal ulceration; both Traverso[7] and Newman[8] have reported patients suffering acute upper gastrointestinal bleeding following the pylorus-preserving procedure.

Recently Beger has reported a subtotal resection of the head of the pancreas with duodenal preservation, showing that the duodenum remained viable despite ligature of vessels close to the duodenal wall. However, 14 per cent of these patients have gone on to have further attacks of pancreatitis[9].

For children with nesidioblastosis a very near total or total pancreatectomy has been performed with preservation of the duodenum[10]. Having performed four such procedures in children with good results the technique of total pancreatectomy with duodenal preservation was extended to younger adults who required a total ablation of their pancreas, following the failure of lesser procedures. This report describes our experiences.

Patients

Between May 1984 and September 1985 a duodenum preserving total pancreatectomy was performed on 14 patients (*Table 1*). There were seven men and seven women whose ages ranged between 19 and 45 years (median, 34 years). All patients had had symptoms of chronic

Table 1 *Case histories*

Patient	Sex	Age	Aetiology	Length of history (years)	No. of previous procedures	Follow-up (months)
1	M	38	Idiopathic	3	3	18
2	M	21	Idiopathic	4	1	18
3	F	19	Choledochal cyst	17	7	17
4	M	33	Trauma	10	5	12
5	F	26	Idiopathic	2	1	12
6	F	38	Abnormal pancreatic duct	6	4	10
7	M	31	Alcoholic	3	3	11
8	F	29	Pancreas divisum	4	2	9
9	F	44	Pancreas divisum	3	3	7
10	F	40	Idiopathic	5	4	7
11	M	27	Pancreas divisum	3	5	3
12	M	45	Idiopathic	9	3	5
13	M	45	Alcoholic	11	3	5
14	F	34	Alcoholic	2	2	5

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pancreatitis, principally pain, the duration of symptoms ranging from 2 to 17 years (median 8·5 years). The aetiology of the chronic pancreatitis was pancreas divisum or other duct anomaly in four, alcohol in three, a choledochal cyst in one and trauma in one, and in five patients no specific cause was identified. No patient underwent this operation as a first procedure. The 14 patients had undergone a total of 46 procedures: 15 subtotal pancreatectomies, 12 cholecystectomies or other biliary procedures, 10 pancreatic drainage procedures including 4 Puestow operations (longitudinal pancreatojejunostomy) and 5 minor or major papilla sphincteroplasties. Four patients had undergone a coeliac plexus block for analgesia. One patient had undergone seven major laparotomies since the age of 2 and was incapacitated by severe pancreatic pain. Six patients were diabetic owing to chronic pancreatitis or previous surgery. The indication for further surgery in all was persistent pain requiring high dose narcotic analgesics (*Table 2*) and the frequency of hospital admissions (*Table 3*).

Methods

A long upper transverse incision was made and a full laparotomy performed to assess the extent of the disease. The pancreas was exposed throughout its length by dividing the gastrocolic omentum outside the epiploic arch and opening the lesser sac. If the distal pancreas had not been resected the body and tail of the pancreas was mobilized in the usual manner, dividing the left gastroepiploic artery near the splenic artery and the short gastric arteries nearer the spleen than the stomach. The head of the pancreas was exposed by dissecting the transverse colon, hepatic flexure and mesocolon off the front of the duodenum and head of pancreas so that the whole of the duodenum was visible. The right gastroepiploic artery and vein which were invariably inseparable from the pancreas were dissected out on the front surface of the pancreas and tied flush with the pancreas. The vessels supplying the duodenal bulb were left undisturbed, receiving their blood from the epiploic arch. All attachments to the front of the pancreas were meticulously cleared and a final assessment of the disease process was made to ensure that duodenal preservation was the appropriate procedure.

Table 2 *Daily analgesic requirement*

Patient	Pre-operation	Present
1	4–600 mg pethidine*	Nil
2	600 mg pethidine*	Dextropropoxyphene/paracetamol
3	2400 mg pethidine*	Nil
4	150 mg pethidine*	Nil
5	400 mg pentazocine*	Nil
6	360 mg dihydrocodeine* 40 mg methadone*	Nil
7	240 mg dihydrocodeine* 15 mg methadone*	180 mg dihydrocodeine* 30 mg methadone*
8	600 mg pethidine*	Nil
9	60 mg morphine* (oral) 600 mg pethidine*	Nil
10	60 mg morphine* (oral) 1000 mg pethidine*	60 mg dihydrocodeine
11	100 mg pentazocine*	Nil
12	300 mg pethidine*	300 mg pentazocine
13	900 mg pethidine*	25–50 mg pentazocine
14	600 mg pethidine* 180 mg dihydrocodeine*	240 mg dihydrocodeine

* Denotes regular requirement
No patient required parenteral analgesia postoperatively

Table 3 *Pre-operative admissions*

Patient	Length of history (years)	Hospital admissions	Total duration of admission (days)	Other admissions of unknown duration
1	3	6	149	2
2	4	12	74	7
3	17	10	345	—
4	10	12	243	—
5	2	10	105	6
6	6	10	67	—
7	3	5	105	—
8	4	6	255	—
9	3	2	102	2
10	5	6	138	3
11	3	7	148	—
12	9	10	157	2
13	11	8	192	5
14	2	4	137	—

Having decided to proceed, the superior mesenteric vein was dissected out down to the point at which it crossed the duodenum. At the angle between the duodenum and the vein, dissection of the uncinate process of the pancreas was commenced using mosquito forceps to dissect out the veins which pass from the superior mesenteric vein to the pancreas. These were tied; a suture tie was often more appropriate than a simple ligature. The vessels were tied as near to the pancreas as possible. Having dissected along the superior mesenteric vein to the neck of the pancreas there was then room to dissect the pancreas off the third and part of the fourth part of the duodenum, starting at the angle between the duodenum and superior mesenteric vein. Each vessel was dissected as close to the pancreas as possible. 'Ligaclips' were invaluable for the smaller vessels. Use of diathermy on the duodenal side was contra-indicated. Care had to be taken to preserve the branches of the superior mesenteric artery, especially posteriorly, which course along the duodenum separate from the pancreas so that a normal blood supply to the fourth part of the duodenum could be maintained. Working steadily along the inner aspect of the fourth part of the duodenum the pancreas was separated off the duodenum so that a finger could be passed behind the uncinate process to lift the gland forwards. A plane between the pancreas and the inferior vena cava was dissected without disturbing or dividing the peritoneal attachments on the outer border of the duodenum, or the small vessels on the posterior border of the duodenum. With the gland lifted forwards the branches of the superior mesenteric artery to the uncinate process could be divided up to the neck of the pancreas. The neck of the pancreas was dissected off the portal vein and the body and tail of the pancreas, if present, were brought to the right so exposing the portal vein. The dissection of vessels from the portal vein and superior mesenteric artery to the pancreas was completed so that a finger could pass from the fourth part of the duodenum along the superior mesenteric and portal veins to the duodenal bulb. This enabled the pancreas to be lifted forwards and to the right and the vessels, branches of the inferior pancreatoduodenal artery passing from the pancreas to the fourth and third parts of the duodenum, to be dissected and divided between clips and ligatures. At a variable point along the second part of the duodenum the ampulla of Vater was encountered. The operator became aware of the approach of the ducts by a dense adherence of the pancreas to the duodenum and a relative lack of larger vessels. The wall of the duodenum, which merges with the bile duct, was carefully followed until the bile duct was encountered. The pancreas was lifted forward and dissected along the posterior border of the bile duct, along which a plane could be developed. The pancreatic duct enters anterolaterally into the bile duct and therefore should be ligated with a non-absorbable suture (6/0 Prolene). The operator had two choices: either to dissect out the bile duct in its entirety or to continue separating the pancreas from the rest of the second and first parts of the duodenum. The most difficult part of the dissection was separating the first part of the duodenum from the pancreas and starting the dissection of the pancreas from the duodenum without damaging the bile duct. Thus, if the bile duct could be easily traced superiorly and separated from the pancreas then this step was undertaken; the dissection of the bile duct was continued to the duodenal bulb at which point the superior pancreatoduodenal artery was encountered. The superior pancreatoduodenal artery was then divided as far away from the duodenum as possible and the pancreas was followed around the first and second parts of the duodenum to the ampulla completely to remove the pancreas. The accessory duct of Santorini was divided during this dissection.

If the bile duct was difficult to dissect the separation of the pancreas from the ampulla to the duodenal bulb was continued, exercising great care to identify the bile duct. Once the bile duct had been defined a plane of cleavage could be developed on its anterior surface and the pancreatic tissue in front of it divided, so exposing the bile duct anteriorly down to the ampulla. Subsequently the bile duct could be freed from the pancreatic tissue to leave an empty 'C' loop, with the bile duct lying unattached within the loop.

The duodenum was usually a dusky blue colour but showed active contraction on stimulation. Haemostasis was secured and omentum placed within the 'C' loop and around the bile duct. Suction drains were placed in the 'C' loop and lesser sac.

The procedure took between 2·5 and 4·5 h to complete. Intra-operative blood loss was 200–900 ml (median 550 ml). In two patients the bile duct was opened during dissection and in one patient the duodenum was opened. The bile duct was repaired with 6/0 polydioxone and the duodenum with two layers of 3/0 polydioxone.

All patients were maintained in the intensive care unit on a ventilator for 12–24 h postoperatively with repeated monitoring of the arterial P_{O_2}, which was maintained above 100 mmHg (13·3 kPa).

The period of postoperative gastric stasis, as assessed by the requirement for a nasogastric tube and intravenous infusion, varied from 7 to 34 days (median 14 days).

The postoperative appearance of the duodenum on barium examination suggests ischaemia (*Figure 1*) but this appearance returns to normal after an indefinite period of time (*Figure 2*). In one patient a cannula was placed in the gallbladder to monitor the appearance of the bile duct (*Figure 3*).

Results

There have been no deaths or acute intra-abdominal complications following this procedure. Five patients developed a septicaemia; in each case this was sepsis related to a central venous line used for parenteral nutrition. The sepsis responded rapidly to removal of the line. Patient 6 had one episode of haematemesis at 15 days. Endoscopy showed no obvious site of bleeding. There was no evidence of ulceration and the duodenum appeared normal in colour with no evidence of ischaemic changes. The haematemesis required conservative treatment only. Two patients developed a postoperative chest infection which required treatment with antibiotics and one patient developed a urinary tract infection. There was one wound infection.

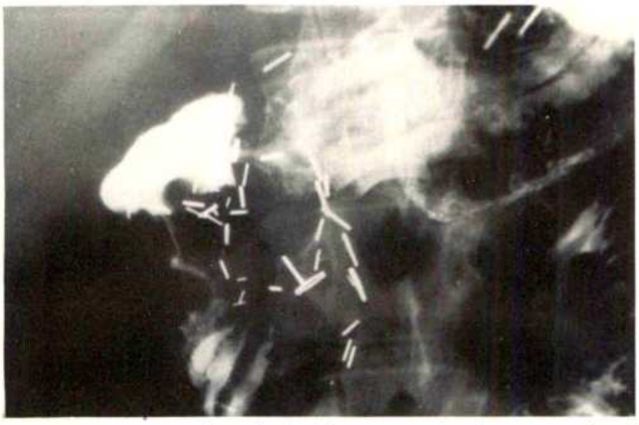

Figure 1 *Barium study in the initial postoperative phase suggestive of duodenal ischaemia*

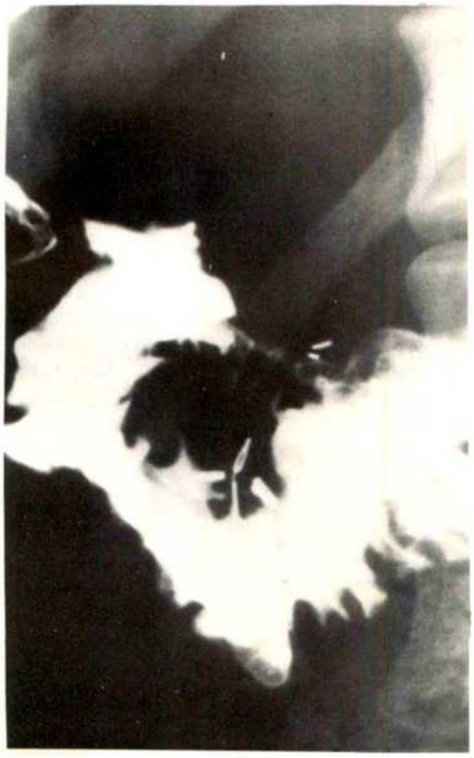

Figure 2 *Barium study (oblique view) showing the duodenal appearance returning to normal*

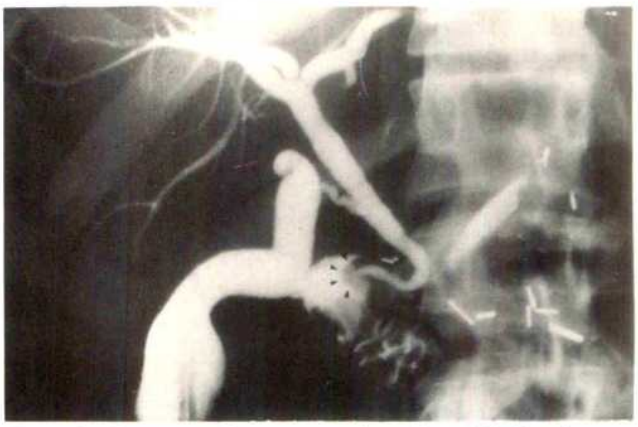

Figure 3 *Contrast study via a cannula in the gallbladder showing a normal bilary tree with flow into the duodenum. Note the ampullary oedema indicated by the arrows*

Difficulty was experienced in the control of diabetes in two patients while in hospital. This was due to failure to control adequately their diet which produced in one significant hyperglycaemia and in the other hypoglycaemic episodes.

In two patients the bilirubin rose outside the normal range postoperatively and in both cases it returned to normal within 2 weeks. The alkaline phosphatase remained within the normal range in five patients. In nine patients the alkaline phosphatase rose outside the normal range within 1 week of the operation. In six the value returned to normal within 1 month. In two the value remained elevated for up to 6 months but is now normal. The bilirubin and alkaline phosphatase remained elevated in one patient who developed a biliary stricture three months after operation. This patient underwent a Roux-en-Y choledochojejunostomy 6 months after his duodenum-preserving operation because of recurrent cholangitis.

Patients left hospital when they no longer required narcotic analgesics and had learned to manage their diabetes. The length of stay in hospital ranged from 17 to 49 days (median 31 days).

Histology of resected pancreatic tissue has shown extensive fibrosis with chronic inflammation.

Follow-up

Patients have been followed up for 3–18 months (median 9·5 months). This represents a cumulative follow-up of 11·6 patient years. Eleven patients have required readmission to hospital postoperatively (*Table 4*), usually short admissions to enable supervision of their diabetes. Six of the fourteen patients have returned to full time work or full time education. Eight have returned to their normal activities, including one patient who successfully completed the 1985 London Marathon 3 months after his operation. The other six patients have not yet returned to work. Nine of the patients no longer require analgesia and none are taking regular narcotic analgesics except as part of a drug rehabilitation programme (*Table 2*). All patients are taking pancreatic enzyme replacement therapy, either Pancrex V Forte (Paines and Byrne Ltd), Creon (Duphar Laboratories Ltd) or Pancrease (Johnson and Johnson Ltd) and generally need to take a greater number of tablets with each meal than pre-operatively to avoid diarrhoea and/or steatorrhoea. Frequency of bowel action is acceptable in 11 patients (*Table 5*). Patient 1 has recently had his dose of Creon increased. Patient 7 has not been taking pancreatic supplements regularly and patient 9 was taking a diet of muesli and yoghurt with inadequate enzyme replacement.

Table 4 *Post-operative admissions*

Patient	Follow-up (months)	Hospital admissions	Duration of admissions (days)	Indication for admission
1	18	3	36	Pain, vomiting drug dependency
2	18	4	55	Pain, vomiting drug dependency
3	17	0	—	
4	12	0	—	
5	12	3	13	Pain, vomiting
6	10	1	7	Hyperglycaemia
7	11	1	7	Drug induced hepatitis
8	9	2	32	Pain, vomiting
9	7	2	Unknown	Diabetic control Psychiatric treatment
10	7	2	15	Pain, vomiting
11	3	1	6	Pain, vomiting
12	5	1	14	Cholangitis
13	5	0	—	
14	5	1	3	Pain

Table 5 *Bowel frequency*

	Pancreatic enzyme replacement (no. of tablets per 24 h)		Diet		
Patient	Pre-op.	Postop.	Pre-op.	Postop.	Bowel frequency (stools/day)
1	48P	60C	L	D	6–8
2	20P	48P	L/D	D	1–2
3	16P	50P	N	D	2
4	40P	25C	D	D	2
5	50P	60Pa	N	D	3–4
6	12P	15C	L	D	1–2
7	—	60C	L	D	5–8
8	30P	60C	L/D	D	2–3
9	20P	24C	L	O	Very loose
10	30P	42C	N	D	0–1
11	40C	60C	L	D	0–1
12	72N	24C	D	D	0–1
13		24C	D	D	1
14	—	44Pa	D	D	1–2

Pancreatic replacement: P, Pancrex V forte; C, Creon; N, Nutrizym; Pa, Pancrease
Diet: N, normal; L, low fat; D, diabetic; O, other

Table 6 *Body weight of patients*

			Weight (kg)		
Patient	Height (cm)	Ideal body weight (kg)	Pre-op.	Present	Percentage ideal body weight
1	185	75·7	85	79·2	104·6
2	181	71·4	68	72	100·8
3	162	54·3	52·4	62·7	115·4
4	188	77·6	69	77	99·2
5	170	59·6	47·4	44·5	93·8
6	178	65·1	74	67	102·9
7	177	69·4	85	95	136·6
8	153	48·5	38·3	41·2	84·9
9	156	51·75	51·5	55·5	107·9
10	158	51·75	72·6	75·2	145·3
11	163	59	51·3	52·6	88·9
12	172	65·75	63·8	67	101·9
13	178	69·4	53	60·7	87·5
14	165	54	57·5	55	101·8

All patients have gained weight postoperatively (*Table 6*). Ten patients are within the range of ideal weight for their sex and height as given for a medium frame in a table of desirable weights for adults[11]. Three others are gaining weight. One patient has recently lost weight owing to poor diabetic control.

Satisfactory diabetic control has been achieved in most patients using a twice daily insulin regime. Two patients use a continuous subcutaneous infusion pump. One patient has required re-admission with an episode of hyperglycaemia due to an upper respiratory tract infection and one patient was having hypoglycaemic episodes owing to irregular meals before using a subcutaneous insulin pump.

Discussion

Duodenal preservation may be a significant advance in the surgery of chronic pancreatitis since the duodenum has important secretory and absorptive functions. Perhaps most important is the preservation of duodenal alkaline secretions to buffer the acidic gastric effluent. It has long been known that secretions from Brunner's glands form a protective lining to the duodenal mucosa[12] and recently Kivilaakso and Flemström have shown that duodenal bicarbonate secretion can increase to maintain chemical neutrality at the epithelial surface and so protect the mucosa against concentrations of luminal acid within the physiological range[13]. Therefore loss of pancreatic bicarbonate, due to pancreatectomy, does not significantly reduce the buffering capacity of the duodenum, whereas duodenectomy and pancreatectomy with consequent loss of all sources of bicarbonate may increase the risk of peptic ulceration which can occur after both Whipple and pylorus-preserving pancreatoduodenectomy[4,7,8,14].

The traditional Whipple and pylorus-preserving pancreatoduodenectomy necessarily involve enteric and biliary anastomoses which contribute to the mortality and morbidity. In Newman's series[8] there was no operative mortality following pylorus-preserving pancreatoduodenectomy for chronic pancreatitis. There was, however, a 25 per cent incidence of anastomotic leakage. The duodenum-preserving operation does not involve the formation of anastomoses, hence this problem does not arise.

Strictures of the choledochojejunostomy have also been reported[1]. Although the duodenum-preserving operation does not involve a biliary anastomosis, one patient has developed a biliary stricture and recurrent cholangitis 3 months postoperatively. There was no injury to the duct noted at surgery so the stricture is probably due to unrecognized trauma or ischaemia.

No patient underwent this operation as a first procedure. Some had undergone previous 85–90 per cent pancreatectomy with resection taken well to the right of the portal vein. Despite this they continued to have severe pain and, like Beger[9] and others[15,16] we believe this is due to continuing pancreatitis. Resection of all remaining pancreatic tissue relieved the patients' pain so that on discharge from hospital none required narcotic analgesia. Subsequent histology has confirmed chronic pancreatitis suggesting that the persistent pain is due to pancreatitis of the small pancreatic remnant left at previous operations. McConnell has made the same observations in patients undergoing total pancreatectomy for chronic pancreatitis after previous lesser procedures[16].

Following this procedure patients are inevitably diabetic; six patients were diabetic before surgery owing to their chronic pancreatitis or previous surgery. No patient has refused surgery after discussion of the implications and proposed management of their diabetes. Close liaison with the diabetologists has been invaluable in the pre- and postoperative management of these patients. In the initial postoperative phase diabetes is controlled with a programmable continuous subcutaneous infusion pump. Once established on a normal diet a twice daily insulin regime is introduced. The patient in whom diabetic control has been most troublesome was found to take an unusual diet. This patient has required postoperative psychiatric treatment and represents a failure of patient selection rather than operative method.

The length of stay in hospital is due in part to the period of gastric stasis together with education in the management of diabetes and weaning from high dose narcotic analgesics. Patients are only discharged home when they no longer require any narcotic analgesia. Unfortunately eleven patients have required readmission postoperatively. This is often because of recurrent 'pancreatic' pain and vomiting (*Table 4*). We have been unable to demonstrate any significant pathology or find any evidence of gastric stasis in these patients. The pain does settle in time, although this may take some months during which time the patient requires considerable support and reassurance. This pain may well be due to the patient's misinterpretation of the usual postoperative discomfort as further pancreatic pain or to 'phantom' pancreatic pain due to autonomic nerve damage in the coeliac plexus or splanchnic nerves.

Delayed gastric emptying is recognized after pylorus-preserving pancreatectomy[17] and, in our experience, occurs initially after the duodenum preserving operation. Initial barium studies of the duodenum show a rather ragged appearance with incoordinate duodenal contractions which return to normal in time. Subsequent studies show a normal appearance and normal gastric emptying.

Duodenum-preserving total pancreatectomy is feasible in the adult and over a follow-up period of up to 18 months is not associated with a high morbidity. We consider it has advantages in terms of preservation of duodenal function with improved long term results over previously described techniques in the surgery of chronic pancreatitis and avoids any anastomoses which in themselves can be a cause of morbidity. Nevertheless, this procedure should be reserved for those patients who require total ablation of their pancreas, and are well prepared for the inevitable diabetes which ensues.

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Intraduct enterokinase is lethal in rats with experimental bile-salt pancreatitis

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Controlled intraduct infusion and peri-acinar dispersal of 100 µl buffer containing sodium glycodeoxycholate (GDOC) at concentrations of 8·5, 17 and 34 mmol/l in rats caused a progressively severe acute pancreatitis from which none of the animals died over the experimental period. Infusion of affinity-purified active human enterokinase in buffer did not cause pancreatitis, presumably because of the inability of the macromolecule to gain access to its specific intracellular substrate trypsinogens. The addition of enterokinase 200 ng to GDOC 34 mmol/l in the infusate resulted in a severe systemic disturbance and a form of acute necrotizing pancreatitis which was uniformly and rapidly lethal. This effect was not seen when equimolar trypsin was substituted for enterokinase. These findings show that enterokinase specifically increases the lethality of experimental bile salt pancreatitis and suggest that this bile-borne enzyme may in some cases pose a significant clinical threat.

Keywords: Pancreatitis, enterokinase

Acute oedematous pancreatitis is pancreatic acinar cell damage associated with the leakage of trypsinogens and other digestive zymogens, together with active amylase and lipase, into the interstitium of the pancreas, peripancreatic tissues, peritoneal cavity and circulation. Pancreatic oedema, abdominal effusion and fat necrosis, as well as elevated enzyme and zymogen levels in blood, occur. Acute necrotizing pancreatitis is a condition in which pancreatic acinar cell damage is accompanied by the specific conversion of trypsinogens to trypsins, at a rate and on a scale sufficient to overwhelm local trypsin inhibitors and other defences. Subsequent tryptic activation of the whole spectrum of pancreatic digestive pro-enzymes results in autodigestion of the pancreas and metastatic enzyme-mediated damage which characterizes a stage in the molecular pathology of the established severe disease[1]. Two mechanisms have so far emerged as initiators of intrapancreatic trypsinogen activation, lysosomal Cathepsin B (EC 3.4.22.1)[2] and bile-borne catalytically-active enterokinase (enteropeptidase EC 3.4.21.9)[3]. The present study in rats examines the conditions under which acute necrotizing pancreatitis may occur experimentally following intraduct administration of sodium glycodeoxycholate and highly purified enterokinase.

Materials and methods

Sodium glycodeoxycholate acid (GDOC) was obtained from Calbiochem, Bishops Stortford, UK. Twice crystallized bovine trypsin and tosyl-lysyl-chloromethyl ketone (TLCK) were obtained from Sigma Chemical Co., Poole, Dorset, UK. Human enterokinase was purified as previously described[4]. Enterokinase inactivated by TLCK was prepared by the method of Grant *et al.*[5]. Leupeptin was kindly provided by Professor H. Umezawa, Institute of Microbial Chemistry, Tokyo, Japan. Amylase was assayed by a chromogenic technique (Phadabas, Pharmacia Diagnostics AB, Uppsala, Sweden).

Controlled pancreatic duct infusion

Male Wistar rats weighing 250–270 g were anaesthetized with intraperitoneal sodium pentobarbitone (6 mg/100 g body weight). The duodenum was delivered through a midline abdominal incision and the distal common bile-pancreatic duct intubated using a 22 gauge Argyll medicut Teflon cannula passed through the intact antimesenteric duodenal wall. The cannula was secured by an encircling suture. During pancreatic duct infusion, the proximal bile-pancreatic duct was occluded by an atraumatic microvascular clip[6]. Each pancreatic duct infusion consisted of 100 µl of 100 mmol/l glycylglycine–NaOH buffer at pH 8 containing 4 mmol/l Ca^{2+} (buffer A) with or without test substances. Duct infusions were delivered by a pump-driven syringe over a two-minute period. The mean infusion pressure in this system was $56 \pm 10·4$ cmH_2O ($n = 36$).

Induction of pancreatitis

The effect of intrapancreatic duct infusion of 100 µl of buffer A alone, or buffer with 8·5, 17, or 34 mmol/l GDOC, or with 200 ng human enterokinase alone, or with 200 ng enterokinase plus 34 mmol/l GDOC, was studied in groups of four rats. After 4 h, the rats were killed and the macroscopic appearance of the pancreas, ascitic volume and amylase concentrations were noted. Blood for amylase and haematocrit was obtained pre-operatively and at 4 h and the percentage fall in plasma volume calculated from the acute change in haematocrit[7]. Three transverse 5 µm formalin-fixed sections of pancreas were examined microscopically by an independent observer and the severity of interstitial oedema, polymorphonuclear leucocyte infiltration, acinar cell necrosis, and haemorrhage were scored on a scale 0 (absent) to 3 (severe) for each section[8]. The sum of the mean score for each parameter was taken as the overall histological quantification of severity.

Time-course of early enterokinase, and GDOC, induced lesions

This study was carried out in two groups of 16 rats after intra-pancreatic duct infusion of 100 µl buffer A containing GDOC 34 mmol/l and either 200 ng active human enterokinase, or 200 ng TLCK-inactivated enzyme. Four rats from each group were killed after 10, 30, 60, and 120 min and the pancreas fixed using intra-arterial 2·5 per cent gluteraldehyde, 100 mmol/l sodium cacodylate buffer, pH 7·2[9]. After fixation, the whole pancreas was removed from the animal, placed in fresh fixative and left for a further 3 h. The tissue was then sliced transversely, washed in the same buffer, post-fixed in 1 per cent osmium tetroxide, dehydrated in ethanol and embedded in a 1:1 mixture of agar 100:Araldite epoxy resin. Complete transverse sections, 2 µm thick were cut on a Reichart-Jong 'Autocut' microtome and stained with 1 per cent toluidine blue in borax for light microscopical investigation[10]. Selected areas were then cut at a thickness of 900 nm on an LKB ultratome III ultramicrotome and stained with uranylacetate and lead citrate for examination in a JEOL JEM 100 CX electron microscope. A detailed light microscopic evaluation was made of each pancreas by an independent observer using the scoring system described previously.

Survival

Survival time in hours was measured in a 8 groups of 12 rats after intra-pancreatic duct infusion of 100 µl buffer A containing one of the following: GDOC 34 mmol/l, enterokinase 200 ng, GDOC 34 mmol/l + enterokinase 50 ng, GDOC 34 mmol/l + enterokinase 200 ng, GDOC 34 mmol/l + enterokinase 200 ng + 2 mmol/l leupeptin, GDOC 34 mmol/l + enterokinase 200 ng + 1 mmol/l TLCK, GDOC 34 mmol/l + 16 ng of active trypsin, GDOC 34 mmol/l + 80 ng of active

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trypsin. Trypsin 16 ng is equimolar, and 80 ng trypsin has a 5-fold molar excess over 200 ng enterokinase in the infusate.

After intraduct administration of the test solutions a femoral vein cannula and a subcutaneous platinum resistance probe sited in the animal's left groin were brought out through a protective tail-collar[11]. The animals were minimally restrained and connected to a constant infusion pump and 6-channel recorder for continuous monitoring of body temperature[12]. Each animal received a continuous IV infusion, of saline containing pethidine 100 μg/ml, and ampicillin in 300 μg/ml, delivered at a rate of 1 ml/h. Survival time was determined by continuous body temperature monitoring as previously described[12].

Statistical analysis was by the Student's two sample t test for comparison of haematocrit, amylase levels, and ascitic volume. Histological grading was analysed using the Mann–Whitney U test where appropriate. Survival studies were evaluated by the log rank test (χ^2).

Results

Pancreatitis was not caused by 100 μl volumes of intraduct buffer A alone or with 200 ng affinity purified active enterokinase. Some pancreatic oedema occurred macroscopically and microscopically but without haemorrhage, acinar cell necrosis or leucocyte infiltration (*Figure 1*). Some elevation of the serum amylase at 4 h (13 500 ± 1291, *Table 1*) was seen from the mean pre-operative level of 8344 ± 1070 1 s.d. ($n = 36$, $P < 0{\cdot}05$), but there was little systemic disturbance or abdominal ascites (*Table 1*). GDOC in the concentrations used resulted in progressively severe pancreatic injury with microscopic haemorrhage, oedema, acinar cell necrosis and leucocyte infiltration (*Figure 1*). At the highest concentration of GDOC used (34 mmol/l), macroscopic haemorrhage in the distribution of the duct system occurred almost immediately after infusion, and within the next 10 min the pancreas appeared oedematous and red. Ascites was noted at all GDOC concentrations and was haemorrhagic in every case. Serum amylase at the end of the 4 h period increased progressively with each concentration of GDOC (*Table 1*), and in each case ascitic amylase concentration was about double the serum level.

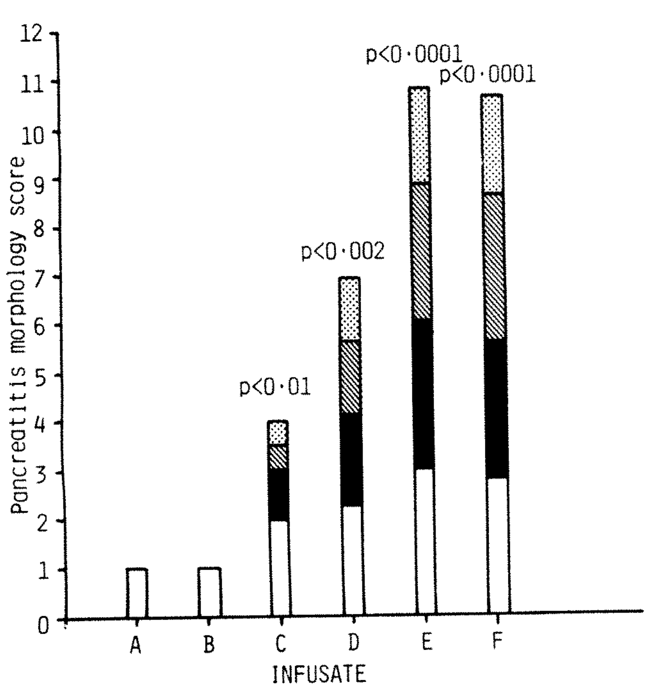

Figure 1 *Morphological severity of pancreatitis 4 h after controlled intrapancreatic duct infusion of 100 μl of: A, buffer alone; B, buffer + 200 ng highly-purified enterokinase; C, GDOC 8·5 mmol/l; D, GDOC 17 mmol/l; E, GDOC 34 mmol/l; F, GDOC 34 mmol/l + 200 ng enterokinase,* P *values for difference from score using buffer alone;* □, *oedema;* ■, *haemorrhage;* ▨, *acinar cell necrosis;* ▩, *PMN-infiltration*

Significant changes in haematocrit and calculated fall in plasma volumes at 4 h were seen for 17 and 34 mmol/l GDOC concentrations. The addition of 200 ng active enterokinase to 34 mmol/l GDOC did not increase the apparently maximal immediate pancreatic injury seen macroscopically and no difference microscopically from 34 mmol/l GDOC alone was seen at 4 h. Higher mean ascitic volumes and amylase concentrations with the enterokinase + bile salt mixture compared with 34 mmol/l GDOC alone were not significant, but the changes in haematocrit and calculated plasma volume were ($P = < 0{\cdot}001$).

Early morphological changes

Over the 2 h period of assessment of early lesions, the findings were indistinguishable whether the 34 mmol/l GDOC infusate contained active, or TLCK-inactivated enterokinase. At 10 min, vascular changes were marked and included widespread and severe congestion of blood vessels. Organizing thrombi were present in most vessels and interstitial haemorrhage was seen. Intralobular ducts were intact but interlobular ducts appeared ruptured. By light microscopy large areas of pancreatic acinar cells showed a decrease in cytoplasmic and granular staining but their nuclei appeared intact. Under the electron microscope the changes in these cells were seen to involve vesiculation and fragmentation of the rough endoplasmic reticulum accompanied by mitochondrial swelling and increase in autophagic vacuoles (*Figure 2*). Zymogen granules were still present. Chromatin in the nuclei of cells showing these changes appeared condensed. Fully necrotic acinar cells were also identified by electron microscopy at 10 min with pyknotic nuclei and an almost total absence of cytoplasmic components. Degenerating zymogen granules were occasionally seen within such cells, but were never seen extracellularly. At 30 min light microscopy showed necrotic pancreatic acinar cells with pale, ghost-like outlines and absence of cytoplasmic organelles. At 60 min perivascular and interstitial polymorphnuclear leucocyte infiltration had begun and fibrin deposits were present throughout the interstitium. By 120 min interstitial leucocyte

Table 1 *Mean values ± 1 s.d.* (n = *4*) *for the parameters studied 4 h after controlled intrapancreatic duct infusion of test solutions.*

Intraduct test solution (mmol/l)	Haematocrit	Percentage fall in plasma volume	Ascitic volume (ml)	Amylase (units/l)	
				Serum	Ascitic
Buffer A	46 ± 0·8	19·4 ± 2·2	0·6 ± 0·1	13 500 ± 1291	30 250 ± 8578
Buffer A + 200 ng enterokinase	46 ± 0·8	19·4 ± 2·1	0·6 ± 0·2	15 750 ± 1707	35 500 ± 9000
8·5 GDOC	46 ± 0·6	20·7 ± 1·9	1 ± 0·1*	19 100 ± 2944†	42 750 ± 12 148
17 GDOC	48·5 ± 1·3*	26·7 ± 3·7*	1·8 ± 0·4†	28 000 ± 2828†	55 750 ± 5674†
34 GDOC	53·3 ± 1·7†	41·7 ± 4·1†	4 ± 0·6†	31 750 ± 3304†	81 750 ± 6652†
34 GDOC + 200 ng enterokinase	64·3 ± 1†	61·6 ± 1·6†	7 ± 2·6†	38 750 ± 11 701†	85 500 ± 10 240†

* $P < 0{\cdot}05$, † $P < 0{\cdot}01$, for values differing from these found after infusing buffer A alone

GDOC, sodium glycodeoxycholate solution

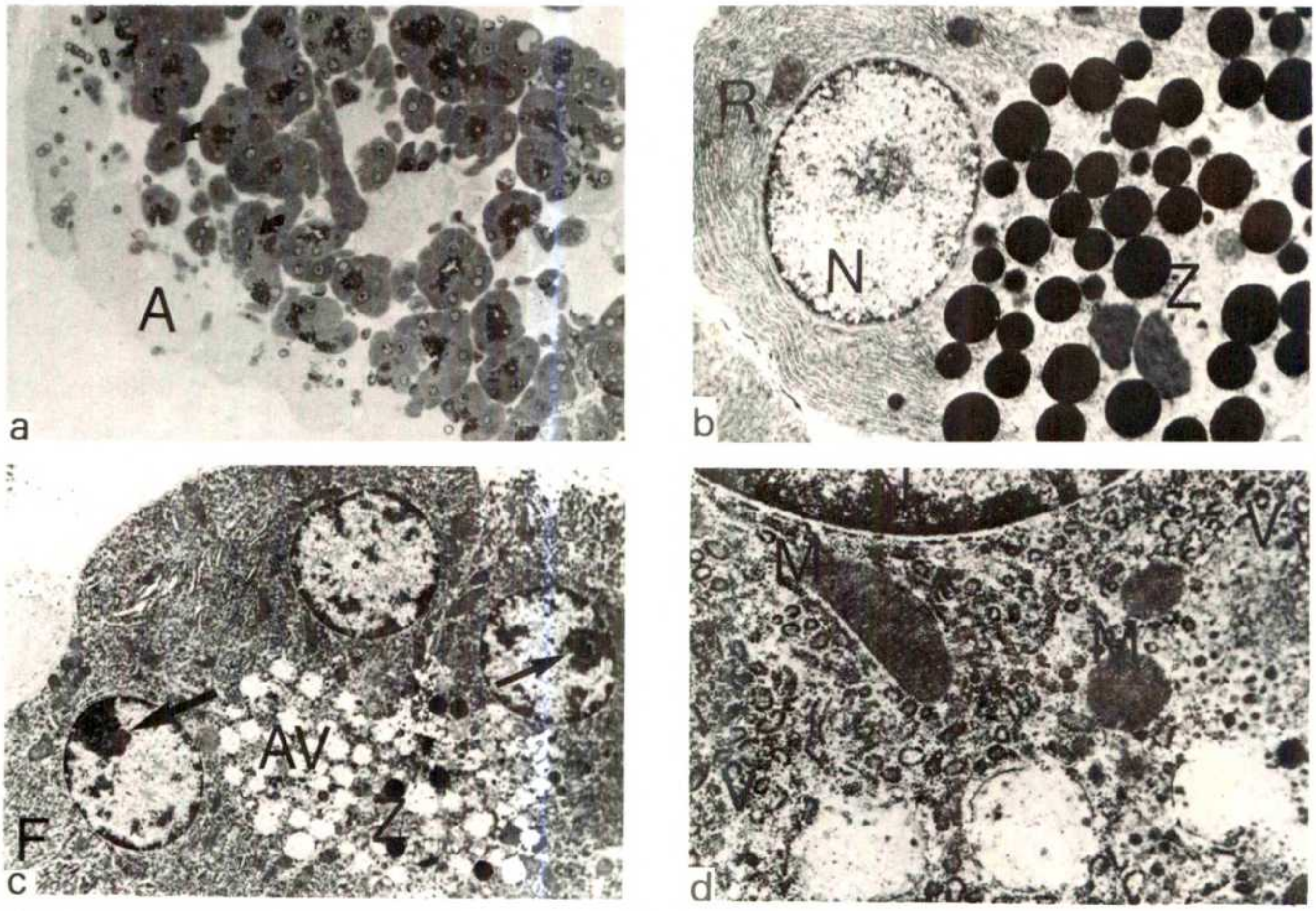

Figure 2 *Morphology of early acute necrotizing pancreatitis.* **a** *Acinar cell necrosis (A) adjacent to acinar cells showing decrease in cytoplasmic and granule staining (arrowed). Toluidine-blue-stained × 270 at 30 min incubation.* **b** *Electron micrograph of normal rat pancreatic acinar cell, rough endoplasmic reticulum (R), basal nucleus (N), zymogen granules (Z) × 7800.* **c** *and* **d** *Injured acinar cells at 30 min incubation showing fragmentation (F) and vesiculation (V) of endoplasmic reticulum, swollen mitochondria (M), autophagic vacuoles (AV) and scanty zymogen granules (Z). × 4700 and × 15 400 respectively*

infiltration was more intense and interstitial haemorrhage more severe. The ultrastructure of the small intralobular ducts was normal for each time point studied.

Survival

None of the rats receiving intraduct active enterokinase alone, GDOC 34 mmol/l alone, or GDOC 34 mmol/l with inactivated enterokinase died within 36 h or within the total period of observation of 54 h (*Figure 3*). All 12 rats receiving GDOC 34 mmol/l + 200 ng active enterokinase together in the infusate died within 36 h (mean time to death 28·3 ± 5·5 h) and 36 h mortality was still 8 of 12 rats when the enterokinase was reduced to 50 ng active enzyme in the infusate (mean time to death 35·8 ± 7·8 h). When active enterokinase was replaced with equimolar active trypsin in the infusate containing GDOC, none of the rats died. The 36 h mortality was 4 of 12 when the amount of trypsin in the infusate was increased to a 5-fold molar excess over enterokinase and the majority of these animals survived >36 h (mean time to death 45·3 ± 19·4 h). Mortality was significantly faster for the group receiving GDOC and 200 ng active enterokinase than for rats receiving GDOC with 50 ng enterokinase or GDOC with a 5-fold molar excess of trypsin in the infusate ($P = < 0{\cdot}05$ and $P = < 0{\cdot}001$ respectively). The apparent difference between the two groups showing lower mortality was not significant ($P = > 0{\cdot}5$).

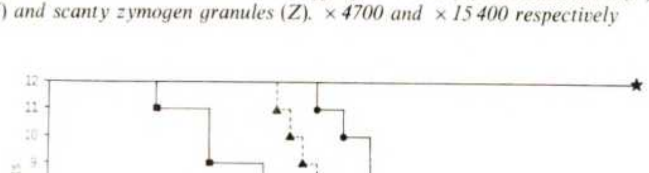

Figure 3 *Survival of animals following pancreatic duct infusion of test solutions.* ■, *34 mmol/l GDOC + 200 ng enterokinase;* ▲, *34 mmol/l GDOC + 50 ng enterokinase;* ●, *34 mmol/l GDOC + 5-fold molar excess of trypsin;* ★, *all other test groups*

Discussion

In this study the standardized infusion of 100 μl of buffer into the rat pancreatic duct system over 2 min generated a mean intraduct pressure of 56 ± 10·4 cmH_2O. The additions to the infusate described did not affect infusion pressure. Other detailed studies in the rat have shown that at intraduct pressures of 20–25 cmH_2O extravasation of pancreatic duct content takes place into the periacinar space[13]. At pressures above 50 cmH_2O, duct rupture occurs and pancreatic injury is determined by the toxicity and quantity of test substance infused[14]. In the present study, this maximal injury was seen as an appropriate experimental system to assess the individual contributions of GDOC and enterokinase in the infusate, to the pathogenesis and severity of the experimental disease. Further studies using controlled intraduct micro-infusion of 50–100 μl volumes of test solutions over 20–30 min, generating intraduct pressures of < 35 cmH_2O are summarized elsewhere[15].

The present study in rats shows that the intraduct and parenchymal dispersal within the pancreas of highly-purified catalytically active enterokinase does not cause acute pancreatitis when enterokinase is given on its own in the infusate. This is presumably because the administered macromolecule is unable to gain access to its intracellular specific substrate tryspinogens, and that activation of what trypsinogen there may be within the duct system at the time of experimental administration is inadequate to initiate the acute haemorrhagic disease. The present study also confirms the toxicity of bile salt within the pancreas[8] and the ability of GDOC to induce experimental haemorrhagic disease at concentrations as low as 8·5 mmol with an apparently maximal insult around 34 mmol GDOC.

The initiation of bile salt induced damage seems likely to include perturbation of duct epithelium[14,16] and of pancreatic acinar cell plasma membranes, as well as intracellular membrane traffic and integrity. Subsequent damage to pancreatic vasculature with morphological features similar to those previously noted with sodium taurocholate[17] may also be involved. That pancreatic digestive zymogen activation presumably by lysosomal enzymes[18,19] also plays a role in the development of the experimental disease is suggested by the electron microscopy findings of degenerating zymogen granules within injured acinar cells, and the absence of recognizable zymogen granules either within dead acinar cells or the extracellular space. The precise identification of the part played by activation of trypsinogens following GDOC administration must, however, await the availability of tests specifically capable of quantifying the activation of these zymogens.

Despite the apparent severity of the morphological changes induced by GDOC 34 mmol, none of the animals died within the experimental period. Perhaps the most noticeable finding of the present study is that the introduction of catalytically active enterokinase into the GDOC-induced lesion results in a form of acute pancreatitis which is uniformly and rapidly lethal. This is despite the apparent absence of any additional morphological features attributable to enterokinase in the early hours of the experimental disease, though the trend to a greater amount of ascites and significant fall in plasma volume at 4 h, suggests the operation and progression of a more severe systemic disturbance. This lethality is directly attributable to enzyme catalysis by enterokinase since acylation of the catalytic site serine hydroxyl[20] or inactivation by leupeptin[21] specifically blocks the effect.

The replacement of enterokinase by equimolar trypsin in the infused GDOC was associated with a return to non-lethal pancreatitis. This is presumably because human enterokinase, unlike trypsin, is resistant to proteolytic degradation[22] or apparent inhibition by potent pancreatic trypsin inhibitors[5] and can activate trypsinogens about 2000 times faster than can trypsin itself[23]. The threat posed clinically by enterokinase-containing bile seems likely to be considerable[3,24].

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Diagnostic value of serum elastase 1 in pancreatic disease

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We studied serum elastase 1 concentrations in patients with pancreatic disease to assess its diagnostic value and compare its sensitivity and specificity with that of amylase and pancreatic isoamylase. Markedly raised concentrations of elastase 1 were found in all twenty-nine patients with acute pancreatitis (amylase was elevated in all but three and pancreatic isoamylase in all but one). Serial measurements of the three enzymes in acute pancreatitis showed that elastase remained elevated longer than amylase and pancreatic isoamylase. The majority of chronic pancreatitis patients studied during a painful relapse (16 out of 21, 76 per cent) had elastase concentrations above the upper normal limit. Amylase and pancreatic isoamylase were elevated in 11 (52 per cent) and in 13 (62 per cent), respectively. Most patients with chronic pancreatitis studied during clinical remission (39 out of 43) had serum elastase levels either within (n = 24) or below (n = 15) the control range. The latter had severe exocrine pancreatic insufficiency and steatorrhoea. In carcinoma of the pancreas, 20 out of 32 (63 per cent) had abnormal serum elastase concentrations; 16 were higher and 4 lower than the control range. Amylase was abnormal in 10 (31 per cent) (8 high, 2 low), and pancreatic isoamylase was abnormal in 16 (50 per cent) (11 high, 5 low). In 46 control patients with non-pancreatic abdominal pain, serum elastase concentrations were not significantly different from those in healthy controls. Elastase was slightly raised in two, whereas amylase and pancreatic isoamylase were elevated in seven and eight, respectively. We conclude that serum elastase 1 is a highly sensitive and specific indicator of pancreatic disease.

Keywords: Acute pancreatitis, amylase, chronic pancreatitis, elastase 1, pancreatic cancer, pancreatic isoamylase, serum pancreatic enzymes

Elastase 1 is a pancreatic proteolytic enzyme which hydrolyses the scleroprotein elastin[1] and has a key role in the pathogenesis of acute pancreatitis[2]. Until recently, attempts to quantify elastase activity in serum by enzymatic methods had failed owing to lack of sufficient sensitivity of the methods used, and the presence of inhibitors in blood[3,4]. However, a specific and sensitive radioimmunoassay technique for serum estimation of elastase 1 has recently become available. In this paper we report the results of a prospective study of serum elastase 1 concentrations in a series of patients with pancreatic disease. The aims of the study were to assess the diagnostic value of serum elastase 1 in acute pancreatitis and other pancreatic diseases, and to compare its sensitivity and specificity with that of the most widely used enzymes amylase and pancreatic isoamylase.

Patients and methods

A total of 243 individuals, divided into five groups, were studied, after informed consent had been given.

Group 1: controls

This group consisted of 72 healthy asymptomatic subjects who were recruited from laboratory and medical staff and from blood donors. There were 50 men and 22 women, with an average age of 46 years, range 18–88.

Group 2: acute pancreatitis

Twenty-nine patients (nineteen men and ten women, average age 61 years, range 13–84) formed this group. All had a history of abdominal pain consistent with acute pancreatitis. In addition, the diagnosis was confirmed at laparotomy in 12, at autopsy in 3, and by ultrasonography and/or computed tomography in the remaining 14. Four of the twelve patients who underwent laparotomy and two of the three who underwent autopsy were found to have haemorrhagic pancreatitis. Fifteen patients had gallstone pancreatitis, four alcoholic pancreatitis, one postoperative pancreatitis, one had pancreatitis secondary to a large duodenal diverticulum occluding the papilla, one metastatic pancreatitis (from lung carcinoma), and the remaining seven had idiopathic pancreatitis. Eighteen of the patients (62 per cent) were studied within 48 h of the onset of pain, seven (24 per cent) were studied on the third day, and the remaining four (14 per cent) on the fourth, fifth, sixth and seventh day, respectively.

Group 3: chronic pancreatitis

There were 64 patients (56 men and 8 women, average age 46 years, range 20–72) in this group. Diagnosis of chronic pancreatitis was based on clinical history[5] and confirmed by radiological evidence of pancreatic calcification in 40 cases, by surgical and histological findings in 14 cases, and by the presence of exocrine pancreatic insufficiency at the secretin–caerulein test[6] and of typical ductal changes[7] at retrograde pancreatography (tortuosity, dilatation and stenosis of the main pancreatic duct, and irregular distribution, dilatation and obstruction of its branches) in the remaining 10. Fifty-eight patients had alcoholic pancreatitis, and the remaining six idiopathic chronic pancreatitis. Forty-three patients (67 per cent) were symptom-free, whereas the remaining 21 (33 per cent) had an acute painful relapse. Twelve patients had pancreatic cysts.

Group 4: pancreatic cancer

Thirty-two patients (twenty-two men and ten women, average age 64 years, range 43–91) were included in this group. Diagnosis was based on clinical data and confirmed at laparotomy in 30 cases, and by retrograde pancreatography and ultrasonography in the remaining 2. In twenty-five patients the tumour was in the head of the pancreas, in one in the body, in two in the body and tail, and in the remaining four it was diffuse

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throughout the whole gland. In all but two, the carcinoma showed local and/or hepatic invasion.

Group 5: non-pancreatic digestive diseases

Forty-six patients with non-pancreatic digestive diseases and abdominal pain were in this group (29 men and 17 women, average age 51 years, range 17–84). The diseases from which they were suffering were the following: acute abdomen (eighteen patients of whom five had intestinal obstruction, six acute appendicitis, four acute gallstone cholecystitis, one perforated duodenal ulcer, and two acute diverticulitis), active duodenal ulcer (eight patients), gallstones (nine patients), irritable bowel syndrome (three patients), postcholecystectomy syndrome (one patient), mesenteric insufficiency (one patient), hepatic echinococcosis (one patient), hepatic carcinoma (two patients), pleural and peritoneal mesothelioma (one patient) and colon carcinoma (two patients). None of these patients had any evidence of pancreatic disease.

Sera from all patients were obtained on admission and stored at −20 °C until the assays were done (generally, within one or two weeks). In seven patients with acute pancreatitis daily blood samples were taken for 7 days from the onset of the attack. In addition to elastase 1, total amylase and pancreatic isoamylase were also measured. Elastase 1 was determined by a radioimmunoassay according to the method described by Satake *et al.*[8]. The assay is commercially available as Elastase 1, Riakit, Abbott Diagnostics (Wiesbaden-Delkenheim, FRG). The immunoassay is highly sensitive and specific for human elastase[8] and gave excellent reproducibility (variances of intra- and interassays <10 per cent). Validation and details of the method are fully described elsewhere[8]. Total serum amylase activity and pancreatic isoamylase were measured by the Phadebas isoamylase test (Pharmacia, Uppsala, Sweden).

Statistical evaluation of data was performed using the Wilcoxon test and linear regression analysis. Gaussian curve distribution of serum elastase 1 concentrations of control subjects was tested by means of skewness and kurtosis coefficients[9].

Sensitivity (true positive) was defined as the number of acute pancreatitis patients with an elevated serum enzyme divided by the number of patients with acute pancreatitis. Specificity was defined as the number of patients (non-pancreatic digestive diseases with abdominal pain) without an elevated serum enzyme divided by the number without acute pancreatitis. Efficiency of an assay was defined as the arithmetic sum of the sensitivity and specificity[10].

Results

Serum concentrations of elastase 1 in the 72 healthy controls showed a log normal distribution and after logarithmic transformation showed a mean of 236 ng/dl and a range of 130–428 ng/dl (mean ± 2 s.d.). No significant relationship was found between serum elastase levels and age and sex in control subjects.

Figure 1 shows the distribution of serum elastase 1 concentrations in the various groups. All patients with acute pancreatitis had clearly elevated elastase levels (range 750–7000 ng/dl). In six patients with acute haemorrhagic pancreatitis diagnosed at laparotomy or autopsy (open circles) elastase values were not significantly different from those of the other patients. Amylase was abnormally high in all but three patients, and pancreatic isoamylase in all but one (*Figures 2* and *3*, respectively). These three normoamylasaemic patients (one of whom also had normal isoamylase) were studied on the third, fourth, and fifth day, respectively, from the onset of the attack.

In patients with chronic pancreatitis serum elastase levels ranged from 45 to 5000 ng/dl. The vast majority of patients studied during clinical remission (39 out of 43) had elastase values either within ($n=24$) or below ($n=15$) the control range. In the remaining four patients serum elastase was above the normal range. Amylase (*Figure 2*) was normal in 37 of these 43 patients, abnormally elevated in 3 (2 of whom also had elevated elastase and pancreatic isoamylase), and abnormally low in 3 (all 3 also had low elastase and isoamylase). Pancreatic isoamylase (*Figure 3*) was normal in 25 of the above 43 patients, abnormally high in 2, and abnormally low in 16 (15 of these had also abnormally elastase low levels). Most of the patients studied during a painful relapse (16 out of 21, 76 per cent) (open circles) had elastase concentrations above the upper normal limit. Of the remaining five patients, four had normal values, and one a subnormal value. Amylase and pancreatic isoamylase were elevated in 11 (52 per cent) and in 13 (62 per cent), respectively (*Figures 2* and *3*). All patients with subnormal elastase and isoamylase concentrations had advanced disease and severe exocrine pancreatic insufficiency with steatorrhoea. In 12 patients with pancreatic cyst, serum elastase concentrations were abnormally high in 9 (75 per cent), whereas amylase and pancreatic isoamylase were elevated in 6 (50 per cent) and in 8 (66·7 per cent), respectively.

In carcinoma of the pancreas, 20 out of 32 (63 per cent) had abnormal serum elastase concentrations: 16 were higher and 4 lower than the control range (*Figure 1*). Amylase was abnormal in 10 (31 per cent) (8 high, 2 low), and pancreatic isoamylase was abnormal in 16 (50 per cent) (11 high, 5 low) (*Figures 2* and *3*). No

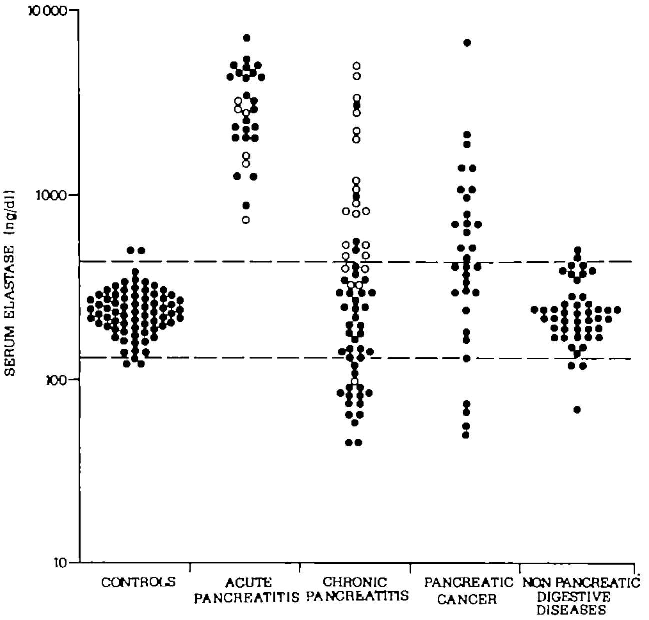

Figure 1 *Serum elastase 1 concentrations in healthy control subjects, in patients with pancreatic disease, and in patients with non-pancreatic abdominal pain. The horizontal dashed lines indicate the normal range. Patients with acute haemorrhagic pancreatitis, and patients with chronic pancreatitis studied during a painful relapse are indicated by open circles*

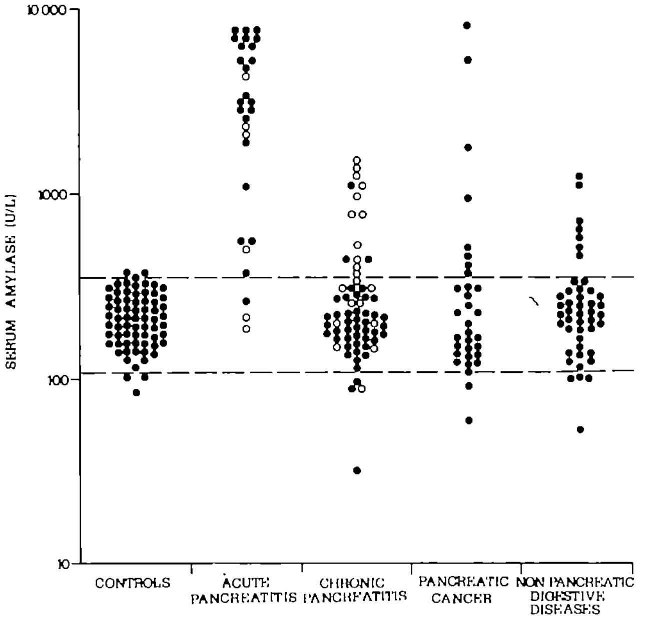

Figure 2 *Serum amylase concentrations in healthy control subjects, in patients with pancreatic disease, and in patients with non-pancreatic abdominal pain. Symbols as in* Figure 1

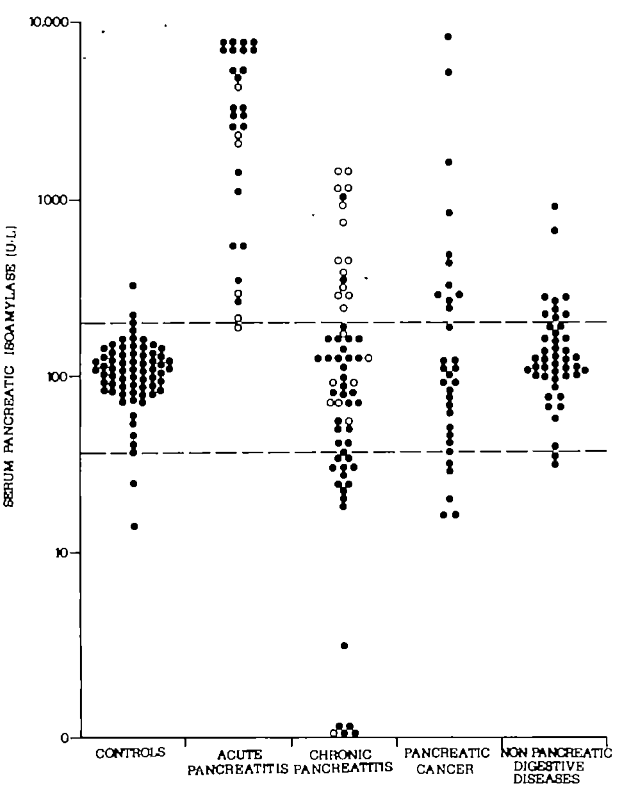

Figure 3 *Serum pancreatic isoamylase concentrations in healthy control subjects, in patients with pancreatic disease, and in patients with non-pancreatic abdominal pain. Symbols as in* Figure 1

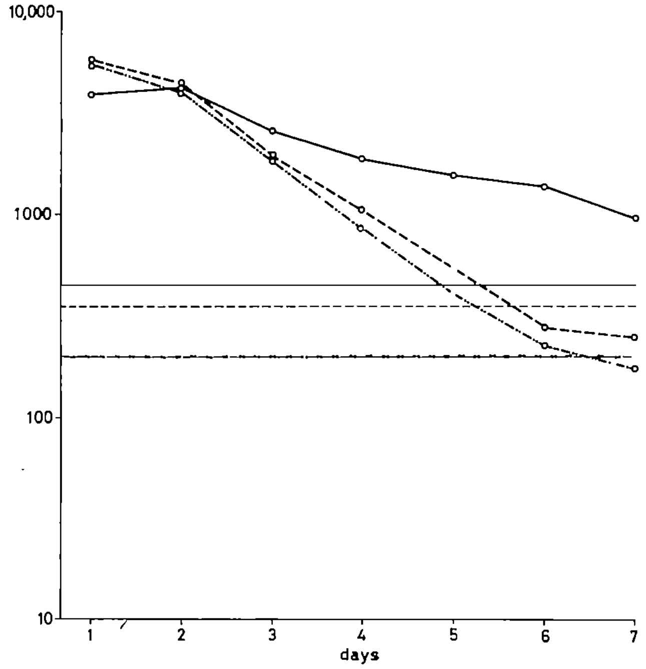

Figure 4 *Serial measurements of serum elastase 1 (ng/dl, ——), amylase (units/l, – – –), and pancreatic isoamylase (units/l, – · · – · · –) in seven patients with acute pancreatitis. Each point is the mean of the values from the seven patients. The horizontal lines indicate the upper normal limit*

relationship between serum elastase levels and the location of the tumour was observed.

In patients with non-pancreatic digestive disease serum elastase concentrations were not significantly different from those in healthy controls (*Figure 1*). Only two patients (one acute suppurative cholecystitis and one intestinal obstruction) had slightly elevated elastase values (450 and 500 ng/dl, respectively; upper normal limit: 438 ng/dl). Amylase (*Figure 2*) was abnormally high in seven patients (one intestinal obstruction, three duodenal ulcer, one postcholecystectomy syndrome, one irritable bowel, and one hepatic echinococcosis). In four of these seven patients, pancreatic isoamylase was elevated. Moreover, the isoenzyme was also elevated in two patients with an acute abdomen, one with duodenal ulceration, and one with gallstones (*Figure 3*).

Figure 4 shows the behaviour of serum elastase 1 and of amylase and pancreatic isoamylase in seven acute pancreatitis patients studied for 7 consecutive days. In all these patients elastase was still abnormally high at the seventh day from the onset of pain, while the other enzymes had returned to normal between the fourth and fifth day in most of them. In six patients pain ceased between the third and fifth day from the onset of the attack, while in the remaining patient pain was still present at the seventh day.

Table 1 summarizes the diagnostic value of serum elastase 1 and of amylase and pancreatic isoamylase in acute pancreatitis. Both sensitivity and specificity of elastase were higher than that of amylase and pancreatic isoamylase.

Discussion

So far, the lack of sensitive and specific methods of serum elastase determination has made a reliable study of serum elastase changes in pancreatic diseases rather difficult. The radioimmunoassay used in this study is the first assay available in clinical practice for the quantitative determination of serum elastase 1. It is specific for elastase 1 or its zymogen, does not cross-react with other proteases, and values measured are not affected by the presence of inhibitors[3,8,11]. The assay takes only 4 h. A main finding of our study is that serum elastase 1 measurement has a very high sensitivity in the diagnosis of acute pancreatitis. In fact, all patients with this condition had unequivocally raised elastase levels. These results do not confirm earlier studies showing a decrease in plasma elastolytic acitivity, when measured by enzymatic methods, in acute pancreatitis[12,13]. They confirm results in dogs with experimental acute pancreatitis[14], and preliminary results in human acute pancreatitis[8] showing a rise in serum elastase levels when measured by radioimmunoassay. In patients with haemorrhagic pancreatitis elastase levels were not significantly higher than those in patients with oedematous acute pancreatitis, indicating that, contrary to what has been reported in experimental acute pancreatitis in rats[15], no relationship exists between the severity of the disease and the degree of the elevation of serum elastase levels. The same has been reported for other serum pancreatic enzymes[16,17]. To assess the specificity of elastase 1 in the diagnosis of acute pancreatitis, we included in the study a large group of patients with non-pancreatic abdominal pain in which pancreatitis may enter into the differential diagnosis. It is of interest that only in two of these patients were serum elastase concentrations elevated, this elevation being very slight. By contrast, amylase and pancreatic isoamylase were abnormally high in seven (15 per cent) and in eight (17 per cent), respectively. Thus, in addition to the very high sensitivity, serum elastase 1 also shows excellent specificity.

Table 1 *Diagnostic value of serum elastase 1, amylase, and pancreatic isoamylase in acute pancreatitis*

	Elastase 1		Amylase		Pancreatic isoamylase	
	No.	%	No.	%	No.	%
Sensitivity	29/29	(100)	26/29	(89·7)	28/29	(96·6)
Specificity	44/46	(95·7)	39/46	(84·8)	38/46	(82·6)
Efficiency	73/75	(97·3)	65/75	(86·7)	66/75	(88)

Sensitivity was determined in 29 patients with acute pancreatitis, and specificity in 46 patients with non-pancreatic abdominal pain. Efficiency is the arithmetic sum of the sensitivity and specificity

Serial measurements of the enzymes in acute pancreatitis indicated that serum elastase remained elevated for longer than did amylase and pancreatic isoamylase. The reason is unclear. Circulating elastase could be metabolized more slowly than the other enzymes, or be released in excess into the circulation for a longer period because of some persisting acinar cell damage. In any case, from a clinical point of view, the determination of serum elastase 1 may be of particular help in those patients with clinically suspected acute pancreatitis, seen for the first time some days after the onset of the attack.

Regarding chronic pancreatitis, an interesting finding of our study was that in the majority of patients with a painful relapse (76 per cent), as well as in most of the patients with pancreatic cysts (75 per cent), serum elastase concentration was abnormally high. Again elastase was a more sensitive indicator of disease activity than amylase and pancreatic isoamylase. In 16 patients with advanced chronic pancreatitis and steatorrhoea, serum elastase concentrations were below the lower normal limit, suggesting that the serum levels of the enzyme may be a fairly reliable reflection of the degree of pancreatic insufficiency in these patients.

Also in pancreatic carcinoma, serum elastase determination provided a greater diagnostic yield, 63 per cent being abnormal compared with 31 per cent for amylase, and 50 per cent for pancreatic isoamylase. All patients had advanced carcinoma, and it would be interesting to know whether serum elastase 1 is also often abnormal in earlier stages of the disease.

In conclusion, the results of this study indicate that serum elastase 1 is a highly sensitive and specific indicator of acute pancreatitis. Its diagnostic value seems to be greater than that of amylase and pancreatic isoamylase not only in acute pancreatitis but also in acute exacerbations of chronic pancreatitis and in pancreatic cancer. Moreover, the tendency of serum elastase 1 to remain elevated for a long period in acute pancreatitis, could allow more reliable monitoring of the course of the disease and, probably, also of the efficacy of the treatment.

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Case report

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Mucobilia: an unusual cause of jaundice

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Floating matter within the biliary tree causing jaundice has been reported in association with, among others, hepatocellular carcinoma, metastatic colonic carcinoma and melanoma[1]. Although mucin secretion is a characteristic microscopic feature of cholangiocarcinoma, profuse mucorrhoea within the extrahepatic bile ducts is rare[2]. We report on a patient with hilar cholangiocarcinoma who presented with intermittent obstruction and cholangitis caused by copious secretion of intraductal mucus.

Case report

A 57-year-old veterinary officer working in Uganda developed pyrexia with rigors in January 1984. Similar episodes accompanied by jaundice and becoming increasingly more frequent followed through to May 1985. On admission to hospital he was jaundiced and pyrexial at 39·0°C. Biochemical tests were consistent with obstructive jaundice. Serology for hydatid, amoebiasis and schistosomiasis was negative. Ultrasonography revealed dilated intrahepatic ducts and percutaneous cholangiography demonstrated a mobile filling defect in the main extrahepatic ducts. At laparotomy in June 1985 a normal gallbladder was removed and the biliary system inspected via the choledochoscope. Thick mucus was found in both right and left hepatic ducts, the common hepatic duct and the common bile duct. No lesion responsible for this secretion was identified. Bile culture yielded *Escherichia coli* and cytological examination of biliary contents was negative for malignant cells. A T-tube was inserted for drainage and saline irrigation. At re-exploration to drain a subphrenic bile collection a week later, more mucus was discovered but no lesion was visualized. Ten days after re-exploration pyrexia and rigors recurred and the patient was referred to the Hammersmith Hospital.

On examination he looked well, was apyrexial and not jaundiced. Liver function tests were normal except for a raised serum alkaline phosphatase (161 units/l). Tubography revealed a filling defect at the confluence of right and left hepatic ducts extending into the right hepatic duct (*Figure 1*). Ultrasonography disclosed normal hilar vessels and an echogenic lesion at the ductal confluence. At operation in September 1985 abundant mucus was noted to float in the extrahepatic ductal system. A slightly raised 1 × 1 cm lesion was obstructing the right posterior sectoral duct and the relevant liver sector was atrophic (*Figure 2*). Local excision was performed and frozen section confirmed complete tumour clearance.

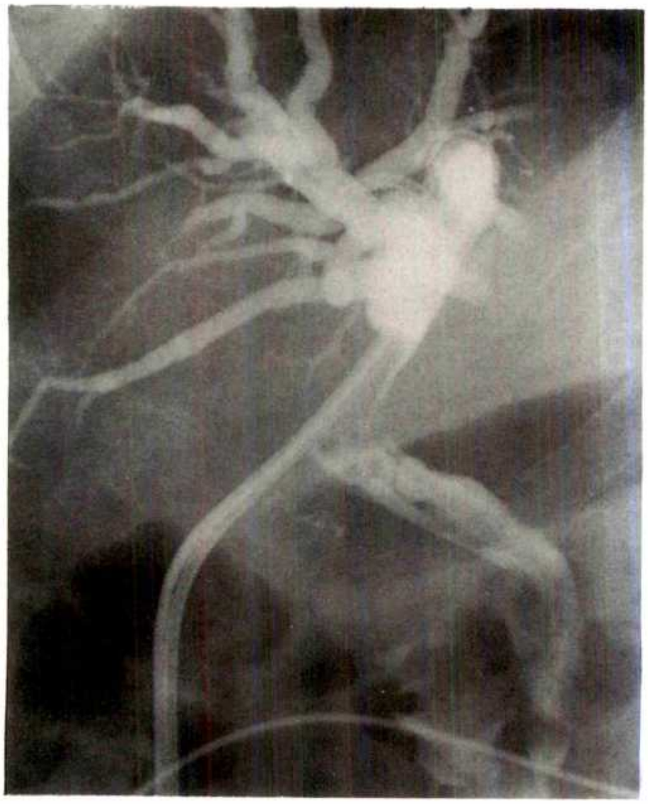

Figure 1 *Tube cholangiogram demonstrating dilated intrahepatic ducts and a large filling defect at the ductal confluence and common hepatic duct. The right posterior ducts are only slightly dilated. Similar defects are seen throughout the extrahepatic biliary tree which is dilated but draining into the duodenum*

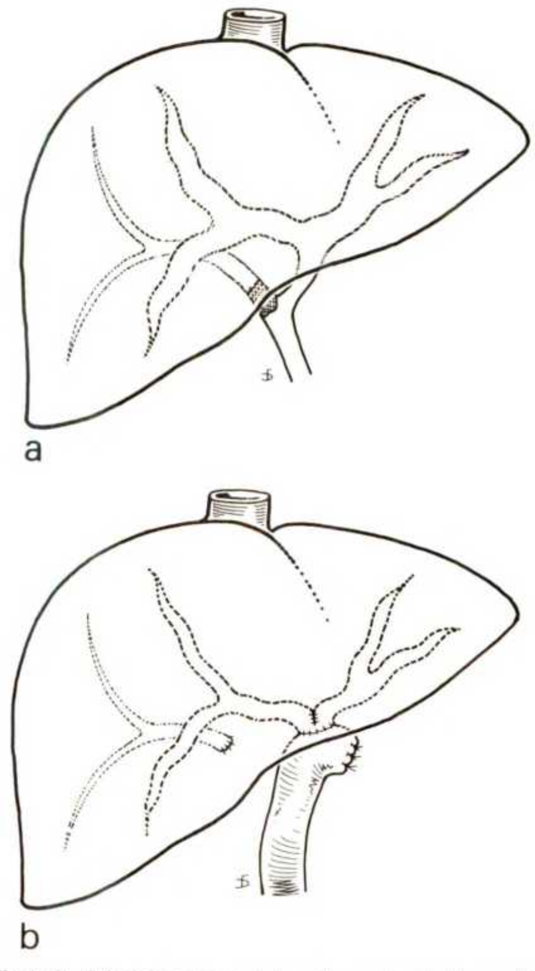

Figure 2 *Schematic representation of operative findings.* **a** *The anterior sectoral duct entered the left hepatic duct. The posterior sectoral duct is obstructed by a tumour. Note dilatation of the intrahepatic ducts with the exception of the right posterior ducts.* **b** *After the tumour was excised, the right posterior duct was oversewn and the right anterior and left hepatic ducts were anastomosed to a Roux-en-Y loop*

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Recovery was uneventful. Microscopic examination showed an *in situ* mucus-secreting adenocarcinoma. Follow-up in October 1985 included a HIDA scan which showed normal uptake and normal excretion of tracer. The patient remains asymptomatic with normal liver function tests.

Discussion

The dilatation of the ductal system distal to the hilar tumour and the temporary resolution of jaundice achieved by biliary irrigation in this case suggest that lumps of mucus rather than the sessile neoplasm was the cause of the obstruction that precipitated the patient's symptoms. Voluminous mucorrhoea is of diagnostic importance and a careful search to identify the offending lesion is imperative. An abundance of intraductal mucus is common with biliary papillomatosis[3], has been reported with a cystic carcinoma of the pancreas[4] and is a feature of biliary mucinosis, a condition characterized by mucous metaplasia of the entire extrahepatic biliary tract[5]. The liquid is rich in albumin and electrolytes, hence the severe electrolytic loss occurring in some cases[5]. Palliation is often inadequate in these conditions as symptoms persist until the cause has been removed[4]. To our knowledge this is the first reported case of obstruction caused by floating plugs of mucus in association with a hilar cholangiocarcinoma.

This case confirms the experience that hilar neoplasms undiagnosed pre-operatively are likely to be missed at laparotomy. Moreover, it illustrates the value of liver atrophy as a reliable indicator of proximal biliary pathology; its recognition at surgery in this patient further strengthened the probability of a lesion indicated in the pre-operative assessment. It is of interest that the segmentally obstructed ducts were not dilated although the rest of the biliary tree bore evidence of a more distal obstruction. As the tumour was completely excised and because of the difficulty and the potential complications of fashioning an anastomosis to a small calibre duct, the posterior sectoral duct was oversewn. In the absence of purulent infection segmental bile duct ligation is unlikely to cause symptoms[6]. The early follow-up of our patient supports that view.

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Note added in proof

A similar report appeared in Gastroenterology (Styne P, Warren GH, Kumpe DA, Halgrim C, Kern F. Obstructive cholangitis secondary to mucus secreted by a solitary papillary bile duct tumor. *Gastroenterology* 1986; **90**: 748–53).

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Mechanism of the haemostatic effect of ethanolamine oleate in the injection sclerotherapy for oesophageal varices

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Changes in coagulation and fibrinolysis were investigated in 20 patients with oesophageal varices, who underwent endoscopic injection sclerotherapy (EIS) with 5 per cent ethanolamine oleate (EO), by means of serial determination of plasma fibrinopeptide A (FPA) and fibrinopeptide Bβ15–42 (Bβ15–42). One hour after the completion of EIS, the value of FPA was significantly increased to 38·1±11·1 ng/ml (mean±s.e.m.) from a pre-EIS value of 7·1±1·4 ng/ml ($P<0\cdot01$) *and it gradually returned to normal range by 48 h after EIS. A very similar change was observed in the value of Bβ15-42* ($P<0\cdot01$)*. These observations indicated that EIS provokes transient activation of coagulation and fibrinolysis.* In vitro *studies, however, revealed that EO inhibits fibrin clot formation because of the* Ca^{2+}*-chelating ability of its constituent ethanolamine, although oleate or benzyl alcohol exhibited procoagulant activity in FPA formation* in vitro. *Nevertheless, an external application of EO or oleate over decapsulized kidney of rat resulted in a significant accumulation of* ^{125}I*-labelled fibrin(ogen). From these results it was suggested that intravascular injection of EO, which exerts an inhibitory effect on coagulation* in vitro, *activates the local coagulation system. The activation may be accelerated by an acute inflammatory process provoked by oleate, which is supported by such clinical manifestations as mild fever, retrosternal pain leukocytosis and an increase in plasma fibrinogen level which was observed in all during the period.*

Keywords: Injection sclerotherapy, oesophageal varices, coagulation and fibrinolysis, fibrinopeptide A and Bβ15-42

Since Crafoord and Frenckner[1] first reported endoscopic injection sclerotherapy (EIS) for oesophageal varices in 1939, this technique has been advocated with excellent results[2–5] in many countries. The haemostatic effect of this method has been thought to be due to thrombi formation in addition to tissue necrosis and inflammation[6,7]. Nevertheless, the precise mechanism of the haemostatic effect of EIS has not yet been fully elucidated, although the formation of thrombi in the very early stage after the injection has been documented in autopsy studies[6,7].

In our institution, EIS with 5 per cent ethanolamine oleate (EO) has been successfully performed to control rebleeding from oesophageal varices, without knowing the exact pharmacological action of the sclerosant. Therefore, the present clinical and experimental studies were conducted to elucidate the mechanism of the haemostatic effect of EO used in EIS.

Patients and methods

Patients

Serial studies were conducted in 20 consecutive patients with oesophageal varices due to liver cirrhosis, who were admitted to the Second Department of Surgery, Osaka University Hospital in 1984 and 1985. There were 16 men and 4 women in the series and mean age was 50·5±6·4 years (mean±s.d.) ranging from 41 to 62 years old. Fourteen patients were Child's grade A, five were grade B and one was grade C. All patients suffered from at least one episode of bleeding due to ruptured varices. Of 20 patients, 17 received EIS for the first time and the rest for the second time.

Procedure of EIS

All patients were given by intramuscular injection atropine sulphate (0·5 mg), hyoscine hydrobromide (20 mg) and pentazocine (30 mg) half an hour before the procedure. EIS was performed without tracheal intubation except in one patient who showed a marked pharyngeal reflex. A Sengstaken–Blakemore (S–B) tube was gently introduced before the endoscopic examination to evacuate gastric contents and to control variceal flow from the stomach. The endoscope used was Olympus B-3 (Tokyo, Japan) attached with a balloon for proximal compression. A 20 G disposable flexible needle was used for the injection. The sclerosant EO was composed of oleate (4·23 g), ethanolamine (0·91 g) and benzyl alcohol (2 per cent) in 100 ml distilled water; an average of 19·4 ml was injected per case ranging from 10 to 27 ml. Just before the injection, the distal and proximal venous flow was controlled by inflating the S–B balloon and the balloon attached to the fibrescope. The sclerosant was injected into varices just above the oesophagogastric junction[8].

Determination of fibrinopeptide A (FPA) and fibrinopeptide Bβ15-42 (Bβ15-42)

Venous blood was collected by the two syringe technique into a 5 ml plastic syringe containing one tenth volume of 0·15 M NaCl solution containing 1000 units/ml heparin and 1000 units/ml aprotinin. Then the plasma was obtained by centrifugation at 2000*g* (4 °C, 15 min). The plasma was defibrinated by ethanol (50 per cent, final concentration) and then diluted five-fold with 0·05 M Tris buffer (containing 0·1 M NaCl, 0·01 M EDTA, 0·1 per cent sodium azide, pH 7·8) to reduce the concentration of ethanol. The diluted plasma was subjected to radioimmunoassay of FPA and Bβ15-42. The radioimmunoassay of FPA and Bβ15–42 was performed basically according to the method of Nossel and Younger[9,10] and Kudryk and Blömback[11] with some modifications. A rapid separation of free antigen from antibody bound antigen was performed by the two antibody method, using polyethyleneglycol[12]. Standard peptides and antiserum were obtained from IMCO, Sweden. Goat anti-rabbit antiserum was obtained from EIKEN Co., Japan. Labelling of FPA and Bβ15-42 with $Na^{125}I$ (Amersham, Japan) was carried out by the chloramine T method[13].

The values of FPA and Bβ15–42 thus obtained in healthy subjects were 4·0 ± 2·1 and 3·0 ± 2·1 ng/ml, respectively (mean ± s.d., $n = 50$). In 20 cases of the present study, serial sampling was performed before and 1 hour, 1, 2, and 3 days after EIS.

Other laboratory tests

Other laboratory tests such as prothrombin time (PT, per cent), activated partial thromboplastin time (APTT), Normotest® (Nyegaard, Norway), plasma fibrinogen, fibrin(ogen) degradation products (FDP) and complete blood cell count were performed in the Central Laboratory of the University Hospital. The above coagulation tests were determined by an automated coagulometer using commercially available reagents. Plasma fibrinogen was determined by thrombin clotting time. FDP was measured semiquantitatively by latex particle aggregation. Normal ranges are as follows: PT, 80 ~ 120 (per cent); APTT, 20 ~ 35 (s); antithrombin-III, 80 ~ 120 (per cent); Normotest®, 70 ~ 150 (per cent); fibrinogen, 150 ~ 350 (mg/dl).

In vitro *study on EO and its constituents*

The effect of EO and its constituents on blood coagulation was studied by means of recalcification clotting time (RCT) and FPA formation. RCT was performed using either fresh citrated whole blood or pooled plasma as substrates. The clotting end point of whole blood RCT and plasma RCT was recorded by the manual hook method and automated Clotek® system (Hyland, USA), respectively. For determination of FPA formed *in vitro*, 250 μl fresh citrated blood was incubated with 50 μl EO or its constituent in a siliconized glass tube at 37 °C for 1 min and the reaction was started by addition of 100 μl 15 mM $CaCl_2$. At designated times, the reaction was terminated by addition of 100 μl 100 mM EDTA and 500 μl of chilled ethanol. And the supernatant of the mixture was subjected to the radioimmunoassay as described above.

Animal experiments

The following animal experiment was conducted by modifying a previously reported method[14]. After anaesthetizing a male Wistar rat, a jugular vein was cannulated and both kidneys were exposed without compromising blood flow. Then a small calibre gamma detector was placed on a sheet of gauze covering decapsulized kidney. ^{125}I-labelled fibrinogen (8 μCi, Green Cross Co., Japan) was injected through the catheter along with 200 mg/kg of *trans*-4-(aminomethyl)cyclohexanecarboxylic acid (*t*-AMCHA), which was given to prevent the activation of fibrinolysis. The accumulation of radioactivity in each kidney was continuously monitored after EO or its constituents were applied to the kidney by soaking into the gauze.

Miscellaneous

All other chemicals were of highest grade available and were obtained from Nakarai Chemicals, Japan.

Statistical analysis

Statistical analysis was performed by Wilcoxon's rank test for comparison between pre-injection values and postinjection values within a group.

Results

Clinical results

Of 20 patients who received EIS, the therapeutic effects such as reduction in the size of varices and vanishing red cherry signs were confirmed in 16 cases by follow-up endoscopic examination performed at 1 week after EIS. There were no changes in the remaining four cases. No bleeding complications were encountered. Minor side effects of EIS such as retrosternal pain (18 cases), microscopic haematuria (8 cases) and low grade fever (14 cases) were encountered, all of which subsided spontaneously within 48 h after EIS. No dyspnoea was noted in any cases, though there was a significant but transient drop in arterial oxygen tension at 1 h after EIS ($P < 0·01$).

Changes in the value of FPA and Bβ15-42 following EIS

As summarized in *Figure 1*, the value of FPA was increased from the pre-EIS value (7·1 ± 1·4 ng/ml, mean ± s.e.m.) to 38·1 ± 11·1 ng/ml at one hour after EIS and returned to the normal range within 2 days after EIS. Also, there was a transient but significant elevation in the value of Bβ15-42 at one hour after EIS.

Changes in other laboratory tests following EIS

As shown in *Figure 2*, the prothrombin value was significantly decreased ($P < 0·05$) from the pre-EIS value of 59·3 ± 3·0 to 51·9 ± 2·4 per cent at one day after EIS. There was a downward trend in the value of antithrombin III and Normotest® at one day after EIS but the differences were not statistically significant.

No changes were observed in the value of APTT, FDP and count of erythrocytes, platelets. Significant leukocytosis was noted at day 1 and 2 after EIS. The plasma fibrinogen level gradually increased to 307·9 ± 22·6 mg/dl at day 3 from pre-EIS values of 252·5 ± 18·3 mg/dl.

Effect of EO and its constituents on recalcification clotting time

To study the effect of the sclerosant used on coagulation, EO or its respective constituents such as ethanolamine, oleate and benzyl alcohol were mixed with citrated whole blood or plasma

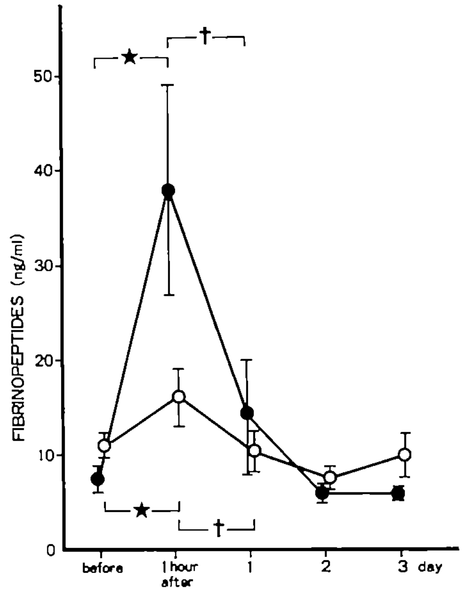

Figure 1 *Changes in values of plasma fibrinopeptides following endoscopic injection sclerotherapy.* ●, *FPA;* ○, *FPBβ15–42.* ★P < 0·01, †P < 0·05

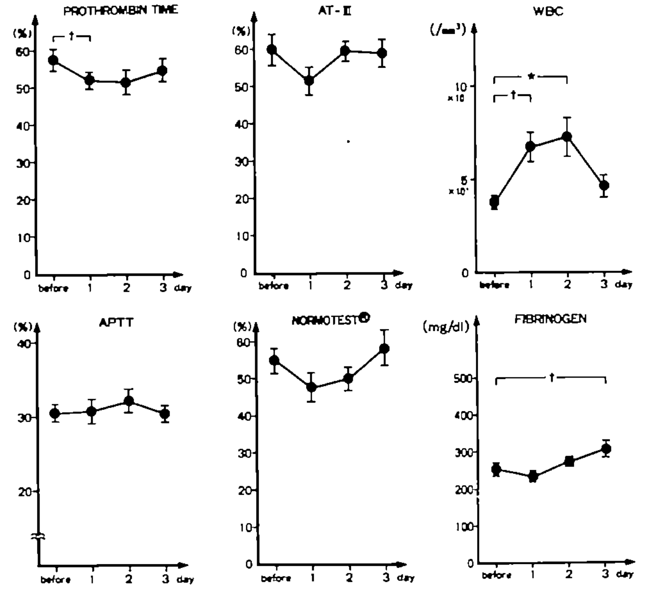

Figure 2 *Changes in coagulation profiles and other laboratory tests following endoscopic injection sclerotherapy.* ★P < 0·01, †P < 0·05

and recalcification time was measured. The results are summarized in *Table 1*. Addition of EO or ethanolamine alone to the citrated whole blood resulted in significant prolongation of the clotting time, while addition of oleate or benzyl alcohol alone to whole blood or plasma resulted in slight shortening of the clotting time. A more marked anticoagulant effect of EO or ethanolamine was observed when it was added to plasma, as the degree of coagulation process by recalcification was more marked in whole blood than in plasma due to the well-known cell-surface mediated acceleration of coagulation.

Effect of EO and its constituents on in vitro *formation of FPA*

To investigate further the effect of EO on coagulation, the effect of EO and its constituents on *in vitro* FPA formation was determined. As in *Figure 3a* FPA formation of citrated whole blood upon addition of $CaCl_2$ was inhibited markedly by ethanolamine, but was accelerated in the presence of oleate or benzyl alcohol. The amount of FPA formed in citrated whole blood by addition of the varied amount of $CaCl_2$ was studied in the presence or absence of ethanolamine. As shown in *Figure 3b*, the inhibitory effect was overcome by increasing the amount of $CaCl_2$, suggesting possible chelation of Ca^{2+} by ethanolamine.

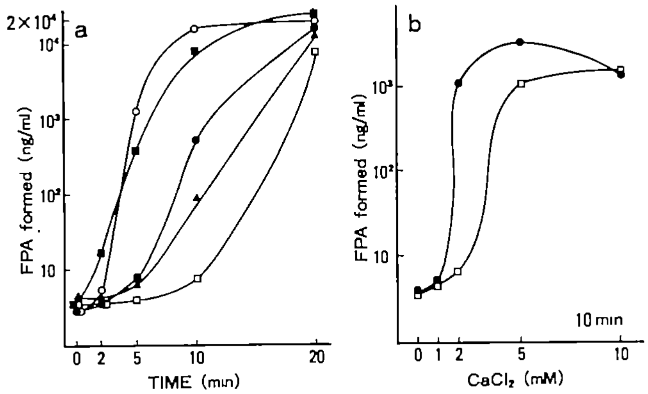

Figure 3 *The amount of FPA formed in recalcified citrated whole blood.* **a** *Effect of the sclerosant and its constituents. Final concentrations of added reagents were as follows:* $CaCl_2$*, 3·8 mM; EO, 0·63 per cent; ethanolamine, 1·1 mg/ml; oleate, 5·3 mg/ml; benzyl alcohol, 0·25 per cent.* ●, H_2O; ▲, *5 per cent EO;* □, *ethanolamine;* ○, *oleate;* ■, *benzyl alcohol.* **b** *Reversal of the inhibitory effect of ethanolamine by increasing amount of* $CaCl_2$ *added. The reaction was terminated at 10 min after the addition of* $CaCl_2$ *as described in the text. Final concentration of added ethanolamine was 1·1 mg/ml.* ●, H_2O; □, *ethanolamine*

Table 1 *Effect of ethanolamine oleate and its constituents on recalcification clotting time*

Reaction mixture*	Final concentration	Clotting time (s)
$CWB+H_2O+CaCl_2$	—	105±4†
$CWB+EO+CaCl_2$	0·56 per cent	227±29
$CWB+E+CaCl_2$	1·0 mg/ml	201±25
$CWB+O+CaCl_2$	4·7 mg/ml	99±3
$CWB+B+CaCl_2$	0·22 per cent	88±3
$PPP+H_2O+CaCl_2$	—	183±6
$PPP+EO+CaCl_2$	1·0 per cent	over 300
$PPP+E+CaCl_2$	1·8 mg/ml	over 300
$PPP+O+CaCl_2$	8·5 mg/ml	177±9
$PPP+B+CaCl_2$	0·4 per cent	192±24

* Reaction mixture for whole blood recalcification clotting time was composed of 200 μl fresh citrated blood, 50 μl reagent or H_2O and 200 μl 25 mM $CaCl_2$; that for plasma recalcification clotting was composed of 100 μl pooled citrated plasma, 50 μl reagent or H_2O and 100 μl 25 mM $CaCl_2$. Calculated final concentration of the respective reagent is shown.
† Mean ± s.d. of three separate experiments
CWB, citrated whole blood; PPP, platelet poor plasma; EO, ethanolamine oleate; E, ethanolamine; O, oleate; B, benzyl alcohol

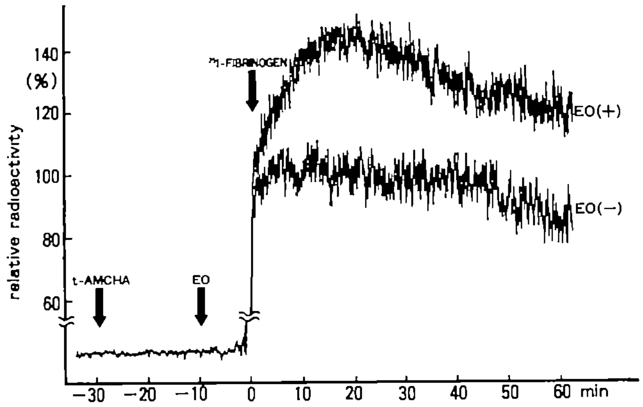

Figure 4 *Accumulation of* ^{125}I*-labelled fibrinogen in the decapsulized rat kidney by an external application of ethanolamine oleate (EO)*

Animal experiments

An external application of EO to the decapsulized kidney resulted in a significantly higher accumulation of ^{125}I radioactivity. A typical recording of ^{125}I radioactivity is shown in *Figure 4*. Ninety minutes after the infusion of ^{125}I-labelled fibrinogen, both kidneys were harvested under perfusion with saline containing heparin and the radioactivity in each kidney was determined by γ-counter. The radioactivity of the kidney treated by EO was 144±38 per cent (mean±s.d., $n=5$), 100 per cent being that in control kidney. The difference was statistically significant ($P<0·05$). The similar increase in the radioactivity was observed in the kidney treated by oleate alone, while no such effect was obtained when it was treated by ethanolamine alone.

Discussion

To investigate the systemic effect of the injected sclerosant on coagulation and fibrinolysis, we have utilized RIA determination of two fibrinopeptides, FPA and Bβ15-42. The former is liberated from fibrinogen by the action of thrombin[9,10] and the latter by the action of plasmin[11]. As the direct measurement of thrombin or plasmin formed *in vivo* has been found to be impossible due to enzyme–inhibitor complex formation, the measurement of the fibrinopeptides is the only sensitive method available at present for the detection of *in vivo* activation of coagulation and fibrinolysis. The conventional coagulation time was not sensitive enough to detect mild hypercoagulability, nor FDP is sensitive to detect fibrinolysis.

In our 20 cases of EIS, there were slight changes in the value of PT, Normotest® and AT-III after EIS. As pre-EIS values of these tests were already abnormal due to liver cirrhosis, it would be difficult to draw any conclusion by the above findings on possible activation of coagulation and fibrinolysis by EIS. However, employing the radioimmunoassay of fibrinopeptides, it was possible to demonstrate clearly the transient activation of coagulation and fibrinolysis after EIS. It was speculated that two possible mechanisms might be involved in the activation by EIS, one is the direct activation of coagulation by EO and another is the activation secondary to inflammatory reaction by the sclerosant[15,16]. The latter possibility is supported by leukocytosis, mild fever, retrosternal pain and increased fibrinogen as acute phase protein. Then, we proceeded to determine the direct effect of EO and its constituents on coagulation. It was a great surprise to observe that EO prolongs clotting time and inhibits *in vitro* FPA formation.

More detailed studies using respective constituents, however, revealed that the anticoagulant effect of EO was due to the presence of ethanolamine, which chelates Ca^{2+} necessary for coagulation. Ethanolamine has been used as a solubilizer of oleate in this particular sclerosant and its anticoagulant effect by chelation has never been reported until now. However, oleate promoted *in vitro* formation of FPA, and it thereby might activate the coagulation directly *in vivo*, if ethanolamine was absorbed in tissue[17,18].

Attempts were made to simulate the effect of EIS *in vivo* by applying EO or oleate directly to decapsulized kidney, where continuous monitoring of the radioactivity of ^{125}I-labelled fibrinogen was performed as reported previously. It was difficult to quantify the result, but application of EO or oleate triggered the accumulation of the radioactivity.

These observations suggest that the sclerosant may directly activate coagulation *in vivo*, although there was no doubt about occurrence of the local inflammatory reaction, which in part contributed to clot formation by the activation of Hageman factor as well as of release of tissue factor[19]. It may not be appropriate to draw any conclusion as to which mechanism primarily accounted for the proved haemostatic effect of EIS but it is apparent that activation of coagulation takes place immediately after EIS, followed by the gradual inflammatory response as shown in the present study by transient elevation of FPA and gradual increase of fibrinogen as the marker of inflammation.

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Primary sclerosing cholangitis: biliary drainage and duct dilatation

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A further extension of the U-tube technique is described in the treatment of six patients with primary sclerosing cholangitis who developed progressive jaundice and recurrent biliary sepsis. All six patients had operative intrahepatic duct dilatation and U-tube placement. Three patients in addition had a Roux-en-Y hepaticojejunal anastomosis. Five patients are improved and are well after a median follow-up period of 56 months. Two patients have had the U-tube removed electively. Three patients with progressive disease required further percutaneous catheter dilatation of intrahepatic strictures via the U-tube tract. Application of the technique permits evaluation of the biliary system by tube cholangiography and provides access in complex cases for repeated therapeutic intrahepatic stricture dilatation.

Keywords: Primary sclerosing cholangitis, U-tube drainage, intrahepatic duct dilatation

Primary sclerosing cholangitis (PSC) is an uncommon chronic inflammatory process characterized by segmental or diffuse fibrosis of the extra- and intrahepatic biliary system. Operative intervention is limited by the narrow calibre, widespread distribution and inaccessibility of intrahepatic strictures. Biliary–intestinal anastomosis has in the past provided relief for extrahepatic strictures but has not resolved the complex problem of intrahepatic bile duct strictures.

The introduction of percutaneous interventional radiological techniques[1–4] has produced a mechanism for treating progressive intrahepatic strictures but requires permanent percutaneous access for repeated manipulation. Experience in Cape Town with transhepatic U-tube stenting in treating irresectable cholangiocarcinoma at the main hepatic duct confluence[5–7] has led to the application of both methods in the management of primary sclerosing cholangitis. We describe a further extension of the U-tube technique including biliary drainage with operative, and, where necessary, repeated postoperative percutaneous dilatation of intrahepatic strictures in a difficult group of patients with PSC and deteriorating liver function, progressive jaundice and repeated sepsis.

Patients and methods

Six patients, (4 men, 2 women; mean age 42 years) had surgery for PSC by one of the authors (J.T.) and have been followed prospectively at Groote Schuur Hospital, Cape Town. The diagnosis was based on the clinical presentation, biochemical profile and radiological features with confirmatory operative and histological findings in all patients. Symptoms of sclerosing cholangitis had been present for a mean of 4·2 years before surgery (range: 6 months–9 years). All six patients were jaundiced, four had cholangitis and two had pruritus and weight loss. Mean serum bilirubin before surgery was 134·5 μmol/l (range: 47–300 μmol/l) with a mean serum alkaline phosphatase of 1158 units/l (range: 322–2370 units/l) (*Table 1*). Serology for rheumatoid factor, antimitochondrial, smooth muscle and antinuclear antibodies and hepatitis B surface antigen were negative in all patients. Endoscopic retrograde cholangiography in five patients and percutaneous transhepatic cholangiography in two patients showed diffuse intrahepatic and extrahepatic beaded stricturing.

Only two patients had inflammatory bowel disease. One patient had chronic ulcerative colitis; the other with Crohn's colitis had required colonic resection for failure of conservative therapy before biliary surgery. Surgical intervention in all six patients was indicated by progressive jaundice with recurrent episodes of cholangitis in four patients.

Operative technique

All patients underwent exploratory laparotomy, during which the liver was biopsied and the biliary tree exposed. The gallbladder was removed, the strictured extrahepatic bile duct opened and biopsy specimens of the duct wall submitted for histology. Mucosal irregularity and accessible strictures were biopsied where possible via choledochoscopy to exclude multifocal cholangiocarcinoma. The first two patients early in the series had careful dilatation of right and left hepatic ducts with a 3 mm Bakes dilator. In the four subsequent patients interventional radiological techniques were used for graduated angiographic catheter dilatation of the hepatic duct bifurcation over a guide wire with fluoroscopy of the biliary system to identify individual intrahepatic strictures. A Lunderquist-Ring biliary torque wire was manipulated through the most proximal stricture which was dilated with a 6 French angiographic cathether over the guidewire. The guidewire was left *in situ* and the 6 French catheter* exchanged for a 7 French Gruntzig catheter† with a 4 mm balloon diameter. The balloon was inflated across the stricture allowing dilatation to 8 times atmospheric pressure. The stricture was re-imaged and the dilatation repeated where necessary. All accessible strictures in both lobes were serially dilated in this manner.

At the completion of intra-operative dilatation, the right hepatic duct was selectively catheterized to facilitate U-tube placement. This was performed as described for cholangiocarcinoma[5–7]. A 3 mm malleable Bakes dilator was guided up the right hepatic duct through the peripheral hepatic parenchyma to the liver surface through an incision in Glisson's capsule. A 16F Ryles tube attached to the dilator was railroaded back through the liver tissue and right hepatic duct to emerge distal to the hepatic bifurcation. Lateral holes were cut in the tubing to allow free intrahepatic biliary drainage and the tube repositioned with holes above and below the hepatic bifurcation. In three patients a Roux-en-Y hepaticojejunostomy was fashioned side-to-side at the hepatic bifurcation over the stent. The ends of the tube were exteriorized through separate stab incisions 4 cm apart in the abdominal wall, the inferior limb of the tube exiting via the blind end of the Roux-en-Y loop attached to the anterior abdominal wall permitting permanent percutaneous access (*Figure 1*). The protruding ends were fixed to each other with a cross piece without attachment to the abdominal wall, allowing tube movement during walking and bending. Two Penrose drains were used to drain potential bile leakage from the liver surface and the biliary tree. In two patients the inferior limb of the U-tube was brought out through the distal common bile duct without construction of a Roux-en-Y hepaticojejunostomy and in the third via the ampulla and lateral duodenal wall. The ends of the U-tube were connected to a T-tube allowing temporary gravity drainage.

Before converting the system to a closed O-tube[7], a tubogram confirmed the correct siting with a flow of contrast from the intrahepatic biliary system into the bowel. After hospital discharge, the tube system was flushed daily by the patient with sterile saline to assist maintenance of patency and to avoid encrustation. The initial rigid tube was replaced electively under general anaesthesia after approximately 6 weeks by railroading a similar size Silastic tube through the tract, using the original tube as a template for the accurate positioning of side holes and skin markers.

**Cook Inc., Bloomingtom, Indiana, USA*
†*Cordis Catheter Corp., Miami, Florida, USA*

Table 1 *Clinical, biochemical and operative data*

				Pre-operative		Postoperative					
Patient	Age	Sex	Symptoms of sclerosing cholangitis before surgery	Total bilirubin (normal: 0–17 μmol/l)	Alkaline phosphatase (normal: 0–115 units/l)	Total bilirubin (normal: 0–17 μmol/l)	Alkaline phosphatase (normal: 0–115 units/l)	Operative procedure	Number of post-operative dilatations	Follow-up	Clinical status
1	53	F	10 months	150	1809	59	1711	Cholecystectomy CBDE + dilatation† U-tube	5	56 months	Improved
2	49	F	9 months	106	1360	59	1176	Cholecystectomy CBDE + dilatation† Hepaticojejunostomy U-tube	4	32 months	Improved
3	24	M	18 months	64	635	20	868	Cholecystectomy CBDE + dilatation† Hepaticojejunostomy U-tube*	0	36 months	Improved
4	47	M	9 years	47	760	40	840	Cholecystectomy CBDE + dilatation‡ Hepaticojejunostomy U-tube	2	8 years	Improved
5	28	M	3 years	300	322	105	1465	Cholecystectomy CBDE + dilatation† U-tube	0	9 months	Died
6	43	M	6 months	140	1500	18	71	Cholecystectomy CBDE + dilatation‡ U-tube*	0	15 years	Improved

CBDE, common bile duct exploration
*, U-tube removed 12 months after surgery
†, Intrahepatic dilatation with Gruntzig balloon
‡, Intrahepatic dilatation with Bakes dilator

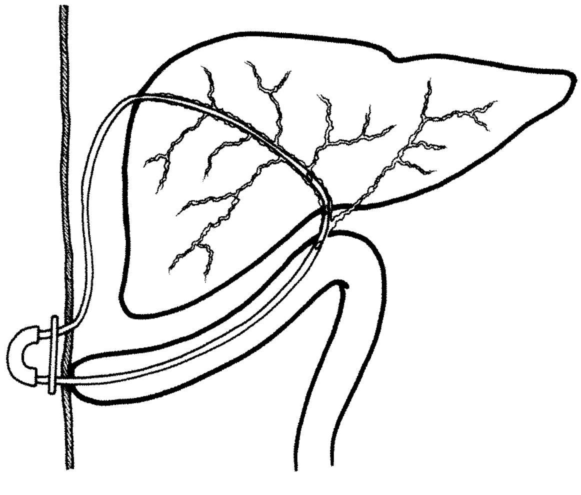

Figure 1 *U-tube and hepaticojejunostomy providing biliary drainage and percutaneous access*

Results

One patient did not benefit and died of progressive liver and renal failure 9 months after surgery. At operation he was deeply jaundiced with advanced biliary cirrhosis and technical difficulty was encountered when dilating the intrahepatic system. Five patients are clinically and biochemically improved and are active, either at home or in full-time employment. Postoperative total bilirubin ranges from 18 to 59 μmol/l (mean 39 μmol/l) and alkaline phosphatase ranges from 71 to 7111 units/l (mean 933 units/l). Duration of follow-up in these five patients is from 32 months to 15 years (median 56 months). Two patients have had the U-tube removed electively 12 months following surgery and both remain anicteric at 3 and 15 years. The more recent of the two patients had severe portal hypertension at operation and has developed oesophageal varices which have required injection sclerotherapy for control on three occasions.

Three patients still have the U-tube *in situ* and have required U-tube replacement on one, five and six instances for tube fatigue, encrustation or blockage. One patient (patient no. 2) has developed portal hypertension and bleeding around the U-tube site due to venous collaterals within the anterior abdominal wall, controlled on two occasions by excision of tissue around the U-tube exit. After initial improvement postoperatively all three patients have again developed progressive jaundice and have required subsequent percutaneous Gruntzig balloon dilatation of multiple intrahepatic duct strictures on two, four and five occasions under general anaesthesia via the U-tube tract (*Figure 2a,b*). This has proved very effective and relatively easy to perform. All three patients have had improvement in the total bilirubin levels following each instrumentation; the alkaline phosphatase levels however remain elevated. Each percutaneous dilatation required a 48 h period of hospital admission with antibiotic cover and was performed without morbidity.

Discussion

The advent of investigative screening techniques and improved percutaneous and endoscopic biliary imaging has allowed earlier diagnosis in PSC without resorting to laparotomy. The natural history, however, remains unpredictable. The diagnosis of PSC may well incorporate a spectrum of diseases. Reports of patients with asymptomatic diffuse biliary stricturing document no further progression histologically on prolonged follow-up[8]. In many, however, the disease is progressive[9,10]. The poor prognosis and failure of current available medical therapy to sustain long term improvement has focused attention on the surgical and interventional radiological alternatives.

Earlier methods in the surgical managment of PSC employed choledochotomy and emphasized prolonged T-tube drainage to maintain patency by splinting the common duct[11–16]. Later favourable reports with biliary decompression[17,18] encouraged a more aggressive approach using choledocho-enteric anastomosis for major extrahepatic obstruction and primary involvement of extrahepatic bile ducts, a technique currently

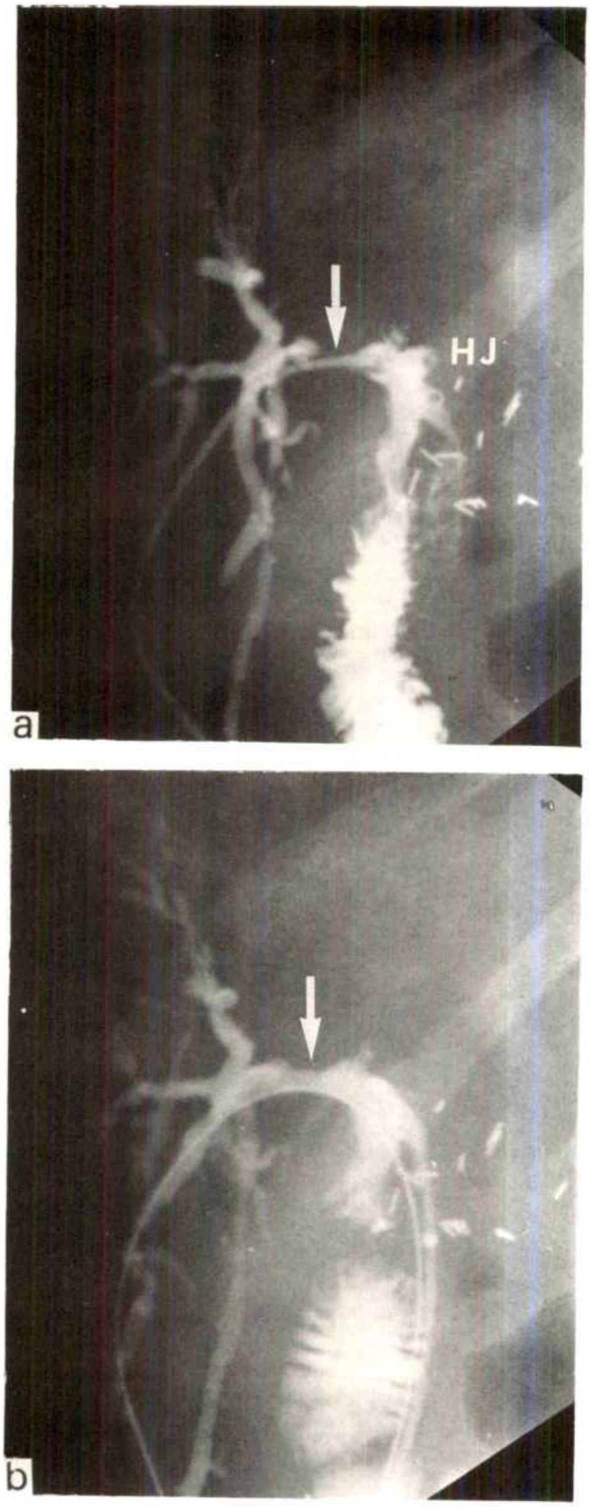

Figure 2 **a** U *tubogram showing hepaticojejunostomy (HJ) and stricture of right hepatic duct (arrow).* **b** *Postdilatation cholangiogram illustrating increased duct diameter at stricture site*

recommended by the Los Angeles group[19]. An innovation has been the use of prolonged transhepatic biliary stenting after colectomy for ulcerative colitis in PSC to promote biliary drainage and reduce biliary sepsis with beneficial results and sustained improvement in all four reported patients after removal of the intrahepatic stents[20]. Observations that the major restrictive lesion in primary sclerosing cholangitis may occur at the hepatic duct bifurcation has led to excision of the hepatic duct bifurcation, operative intrahepatic biliary dilatation and biliary reconstruction using bilateral hepaticojejunostomies with long-term Silastic transhepatic stenting[21]. Nine of the ten reported patients responded with decreased bilirubin during follow-up at 4–36 months.

The technique described in this paper is simpler and of considerably less magnitude than excision of the extrahepatic ducts including the hepatic duct confluence. The common hepatic duct is merely opened, the major and smaller ducts are dilated and access for subsequent dilatations ensured by placing a U-tube with or without a hepaticojejunostomy with the blind jejunal loop brought up to the peritoneal surface of the abdominal wall. Because this simpler technique is successful, the authors can see no justification for the major operative intervention required to excise the hepatic duct confluence as suggested by Cameron *et al.*[21].

A major limitation in the past has been the relative inaccessibility of the intrahepatic biliary tree, the diffuse involvement and the progressive nature of the disease affecting major central and smaller peripheral ducts. A novel technique in managing complex intrahepatic strictures has been the formation of a stoma providing permanent biliary access without resorting to a major operative procedure. Therapeutic intervention through the cutaneous jejunostomy via the proximal limb of a Roux-en-Y hepaticojejunostomy allows dilatation of strictures, intraductal stent placement and stone extraction[22,23]. The early experience of the Miami group demonstrated the technical feasibility of repeated external access and dilatation in PSC through the stoma[22]. Problems with bile leakage have led to modification of the permanent-access hepaticojejunostomy technique with the fashioning of an antireflux valve. This, too, has not been ideal and the authors have suggested that delayed closure of the stoma and subcutaneous placement may be more convenient, providing access if required at a later stage[23]. We have preferred to place the jejunal loop deep to the abdominal muscles but adjacent to the anterior abdominal wall. If marked with metal clips (unpublished data, J.E.J. Krige), repeated percutaneous access can be achieved under local anaesthetic even if no U-tube or transhepatic tube is left *in situ*.

The Cape Town procedure employs operative proximal biliary drainage of extrahepatic strictures and intra-operative radiological imaging combined with catheter and balloon dilatation of major intrahepatic duct strictures over a guidewire. The narrow fibrotic ducts in PSC make blind intra-operative instrumentation hazardous with potential ductal injury. By incorporating radiological techniques, the controlled dilatation over a guidewire minimizes the danger of ductal injury or false passage formation, allowing progressively smaller peripheral lesions to be dilated.

A critical issue is the effectiveness and required frequency of percutaneous dilatation for intrahepatic strictures[22]. Recurrence may be rapid in complex cases necessitating repeat dilatations at one or two monthly intervals[22]. Prolonged transhepatic stenting in the Cape Town experience promotes free biliary drainage and allows easy and rapid cholangiography while assessing the natural history and progression of the intrahepatic disease. The optimum duration of stenting after surgery remains controversial. The advocates of prolonged stenting report excellent results with tubes left *in situ* for 12–16 months[20–22]. The Los Angeles policy has been to individualize the duration of stenting determined by the anatomic location of the major strictures, degree of scarring, adequacy of the anastomosis and the clinical and cholangiographic response to therapy[19]. Two patients in the present series had elective removal of the U-tube at 12 months without subsequent clinical progression of the disease over prolonged follow-up at 3 and 15 years. These patients may represent the benign end of the disease spectrum. Three of our patients with progressive disease have the U-tube remaining *in situ* and have required intermittent percutaneous dilatation on two, four and five occasions; the patients with more aggressive disease benefiting from dilatation at approximately 4 monthly intervals. The actual dilatation in PSC appears to be easier than with secondary or post-inflammatory sclerosing cholangitis (unpublished data, J. Terblanche).

In this series fluoroscopic control and catheter manipulation over a guidewire has allowed intrahepatic dilatation without morbidity. Haemobilia, bile leakage, bacteraemia and liver abscess are reported complications after percutaneous transhepatic biliary drainage and instrumentation[24,25]. No complications have occurred using a larger and softer 14F Silastic tube for long-term transhepatic stenting, other than cholangitis due to tube occlusion or side hole encrustation which is managed simply by replacing the system. Compliance with daily tube maintenance following the appropriate tuition has ensured individual long-term patency and has allowed all our patients to resume full economic and domestic activities.

The Cape Town experience suggests that biliary decompression, prolonged U-tube stenting and intrahepatic duct dilatation may provide beneficial palliation in the small group of complex patients with PSC who have progressive jaundice and deteriorating liver function despite medical therapy.

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Nipple preservation during mastectomy

In a retrospective study of 100 patients with operable breast cancer, microscopic involvement of the nipple–areola complex was found in 16 cases. Each of these 16 cases occurred in patients with centrally situated tumours. In contrast, nipple involvement did not occur with peripherally situated tumours lying >2 cm outside the areolar margin ($P<10^{-6}$, Fisher's exact test). Nipple involvement was more likely in patients with ≥ 4 positive axillary nodes ($P<0{\cdot}01$, χ^2 test). From this study it appears that nipple preservation may be undertaken during mastectomy for small peripheral tumours, provided the nipple is clinically normal, and frozen section analysis of the sub-nipple area is shown to be free from tumour invasion. These criteria for nipple preservation were satisfied in 20 patients out of a prospective series of 60. In this group, nipple preservation on the skin flap improved the cosmetic result of breast reconstruction in 35 per cent, and facilitated skin closure in 20 per cent. After a mean follow-up period of 50·4 months, nipple preservation was not associated with any significant excess of local recurrences.

Keywords: Breast cancer, nipple involvement, nipple preservation

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Removal of the nipple has been regarded as an essential feature of mastectomy for cancer. The basis for this was the description of lymphatic drainage of the breast tissue towards the nipple and then onward via the sub-areolar plexus of Sappey[1]. More recent work, particularly that of Turner-Warwick, has emphasized that this pattern of drainage is incorrect[2].

Preservation of the nipple is of importance because of the increasing role of reconstruction following mastectomy. Although the nipple–areolar complex can be reconstructed from a variety of tissues, none of these produce a result as good as use of the real nipple[3–5].

It is possible either to retain the nipple on the chest wall as in a subcutaneous mastectomy[6] or alternatively to 'bank' the nipple on the thigh or abdomen[2,3]. The latter tactic has fallen into disrepute following case reports of tumour developing in transplanted nipples[7–10]. Pleas for saving the uninvolved nipple demand a careful examination of the incidence of nipple involvement in stage I and II breast cancer.

In the first, retrospective part of this study we carried out an analysis of nipple involvement in 100 patients in order to identify those in whom it would be safe to preserve the nipple-bearing area. In the second, prospective part we used these findings to assess the outcome of nipple preservation in 60 consecutive patients.

Patients and methods

Retrospective study

A retrospective analysis of 100 consecutive cases of operable breast cancer was carried out in order to determine the frequency of nipple involvement and the relationship between nipple involvement and tumour size, tumour position and axillary nodal status. All patients had a modified radical 'Patey' mastectomy without postoperative radiotherapy. For the purpose of this study the breast was divided into two zones: a central zone (zone A) encompassing the nipple–areolar complex and a 2 cm surrounding disc of breast tissue, and a peripheral zone (zone B) comprising the remainder of the breast. Following review of the clinical history each tumour was assigned to zone A or zone B. The histological blocks on each tumour were reviewed and the following features were noted: maximum diameter of the primary tumour (mm), status of the axillary lymph nodes, and encroachment of tumour towards the nipple. The last aspect was assessed by examining two sagittal sections through the nipple bearing area. This was deemed positive if tumour infiltrated to within 5 mm of the surface of the nipple.

Prospective study

Using the criteria described in the results of the retrospective study, nipple preservation was assessed prospectively in 60 consecutive patients with operable breast cancer. Informed consent was obtained. The nipple bearing area was carefully examined to exclude macroscopic abnormalities; tumour size and distance from the edge of the nipple was measured with callipers and the position of the tumour was classified according to its zone. In patients with clinically normal nipples and with tumours of <5 cm situated in the peripheral zone, tissue from the sub-nipple area was sent for frozen section analysis during mastectomy. If this was tumour-free, nipple preservation was carried out. A modified radical 'Patey' mastectomy was carried out in all cases. When the nipple was preserved, skin over the tumour bearing area and at least a 2 cm margin of surrounding normal skin was resected in such a way as to leave the nipple at the free edge of either the superior or inferior flap. The technique of mastectomy was otherwise unaltered save for the use of fine interrupted sutures to oppose the nipple to the other flap. The retention of the nipple–areolar complex at the centre of the wound together with retention of a relative excess of skin produced a result that would, if desired, facilitate subsequent reconstruction.

Results

Retrospective study (Table 1)

Of 41 tumours situated within the central zone, 16 (39·0 per cent) had extension of tumour into the nipple area. In seven instances this area was invaded by infiltrating duct carcinoma, in three

Table 1 *Retrospective study: factors related to nipple involvement*

	Nipple involved	Nipple tumour-free
n	16	84
Zone A (central)	16 (39·0%)	25 (61·0%)
Zone B (peripheral)	0	59 (100%)*
Mean tumour diameter (mm)	39·88 ± 19·93	31·72 ± 14·56†
Positive axillary nodes	9 (56·3%)	35 (41·7%)‡
>4 positive axillary nodes	6 (37·5%)	9 (10·7%)§
Flap recurrence	4 (25%)	6 (7·1%)¶
All recurrences	8 (50%)	30 (35·7%)‡

*$P<0{\cdot}000001$ (Fisher's exact test), † non significant (Student's *t* test), ‡ not significant (χ^2 test), § $P<0{\cdot}01$ (χ^2 test), ¶ $P<0{\cdot}05$ (χ^2 test)

Based on a presentation to the Surgical Research Society, London, 1982

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cases intraduct tumour alone was present (two of these being associated with Paget's disease) and in the remaining six nipples both infiltrating and intraduct tumour was present (two of these being associated with Paget's disease). Six (37·5 per cent) of the microscopically abnormal nipples were clinically abnormal.

In contrast none of the 59 tumours situated in the peripheral zone had extension of tumour towards the nipple. This distribution is highly significant (Fisher's exact test, $P<0{\cdot}000001$).

Involvement of the nipple was associated with an increased incidence of $\geqslant 4$ positive axillary nodes (χ^2 test, $P<0{\cdot}01$). Although the tumour size was larger when the nipple was involved this difference did not reach statistical significance.

After a mean follow-up period of 7·5 years (range 5·8–9·7 years), patients with involvement of the nipple had a significant increase in skin flap recurrence (χ^2 tests, $P<0{\cdot}05$), although their overall recurrence rate was similar to patients without nipple involvement.

From these results, and from data reported by others[5,11–19], criteria for nipple preservation were formulated for evaluation in a prospective study. These were: a clinically normal nipple; tumour situated in the peripheral zone, tumour size of <5 cm and negative frozen section analysis of the sub-nipple area at the time of mastectomy.

Prospective study

The nipple was removed in 40 patients. Of these, the nipple was clinically abnormal in five patients (12·5 per cent), was histologically invaded by infiltrating duct carcinoma in eight cases (20 per cent), and the skin over the tumour (but away from the nipple) was invaded in two instances (5 per cent). One patient had an abnormal looking nipple that was histologically free of tumour.

The nipple was preserved in the remaining 20 patients. All had a clinically and histologically normal nipple and a negative frozen section analysis of the sub-nipple area. In one case (5 per cent) the skin overlying the tumour was invaded by infiltrating duct carcinoma.

The mean tumour diameter in cases where the nipple was preserved was $22{\cdot}2 \pm 8{\cdot}4$ mm whereas in those where the nipple was removed it was $28{\cdot}2 \pm 11{\cdot}3$ mm. This difference was significant at the 5 per cent level (Student's t test). There were no significant differences in the age, menopausal status, or pathological lymph node status between the two groups of patients.

Seven of the patients (35 per cent) who had preservation of the nipple have had successful subsequent breast reconstruction by the insertion of a sub-pectoral silicone prosthesis (*Figure 1*). In four patients (20 per cent) with particularly eccentrically placed tumours, preservation of the nipple on the skin flap facilitated skin closure.

Immediate complications of nipple preservation occurred in four patients. Two (10 per cent) suffered partial thickness nipple loss which later healed by primary intention, and a further two patients (10 per cent) developed full thickness nipple loss which necessitated excision and skin grafting.

The mean follow-up period of the patients in the prospective study is 50·4 months (range 37–61). The survival patterns of these patients are shown in *Table 2*. Flap recurrence has occurred in two patients (10 per cent) who had nipple preservation and in one patient (2·5 per cent) who had the nipple removed. Although it is difficult to draw statistical conclusions from these findings, it seems that preservation of the nipple has not, to date, been associated with a significant excess of flap recurrences.

Flap recurrence. One patient who had preservation of the nipple later developed recurrence within the retained nipple itself. This patients' original tumour was a 25 mm infiltrating duct carcinoma situated within the peripheral zone. Eighteen months after mastectomy she developed a bloody discharge from the retained nipple which was found to be due to intraduct tumour within the major ducts. This was managed by local excision and irradiation. Further flap recurrence occurred 12 months later which was managed by chemotherapy and radioactive gold grain implantation. At the present time she is free from further metastases, 54 months after mastectomy. A second patient developed flap recurrence 12 months after mastectomy with nipple preservation. In this instance the nipple itself was free of tumour. This was managed by local excision and irradiation. This patient is free from further recurrence 56 months after mastectomy.

One patient developed flap recurrence 24 months after mastectomy with excision of the nipple bearing area. This was managed by local excision, radiotherapy and tamoxifen. She is free from distant disease 48 months after mastectomy.

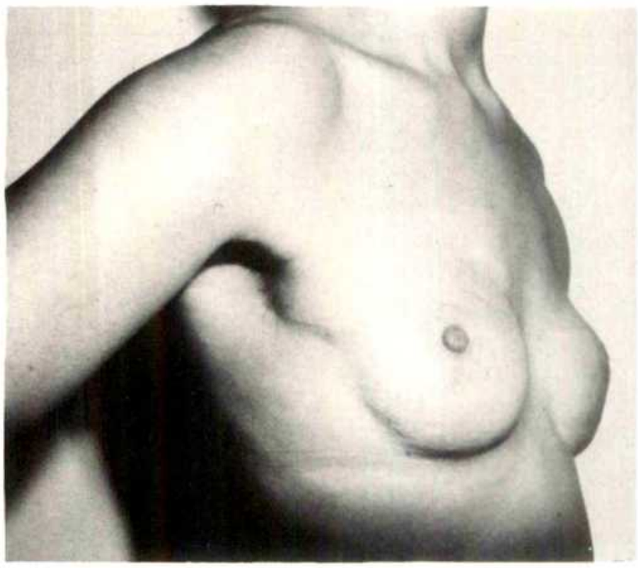

Figure 1 *53-year-old with a $T_1N_0M_0$ carcinoma of the upper outer peripheral zone of the right breast. The nipple was preserved on the inferior flap and the breast reconstructed six months later*

Table 2 *Prospective study: recurrence rates after nipple preservation* versus *nipple excision*

	Nipple preserved	Nipple removed
Number	20	40
Nipple recurrence	1 (5%)	—
Flap recurrence	1 (5%)	1 (2·5%)
Distant recurrence	5 (25%)	12 (30%)
All recurrences	7 (35%)	13 (32·5%)

Discussion

The surgical management of operable breast cancer may be either by wide local excision or mastectomy. The efficacy of each in terms of local control and overall survival still requires longer follow-up studies. As cosmetic and psychological considerations gain importance the frequency of nipple involvement is relevant to both conservative and radical surgical procedures. Following mastectomy there is an increasing demand for breast reconstruction. Here, preservation of the nipple can significantly improve the cosmetic result. After breast conservation it is important to establish the risk of flap recurrence associated with retention of the nipple area.

Several previous studies have investigated the incidence of nipple involvement and their findings are summarized in *Table 3*[5,11–19]. The overall frequency of nipple involvement varies from 8 per cent to 50 per cent. Infiltrating tumour is present within the nipple in 5·6 to 22·5 per cent of cases, whilst non-invasive neoplastic elements are present in 3 to 27·5 per cent. Although there appears to be general agreement that a clinically abnormal nipple is commonly involved with tumour, it seems

Table 3 *Nipple involvement: a literature review*

Principal author	Smith	Parry	Lagios	Andersen	McCarty	Wertheim	Quinn	Pettinato	Morimoto	Kissin
Year	1976	1977	1979	1979	1980	1980	1981	1984	1985	1986
Number	541	200	149	40	291	1000	44	1000	141	100
No. of nipple sections	2	serial	serial	14	serial	8	27	serial	serial	2
Nipple defined positive to depth (mm)	5	5	4	10	3	?	10	10	20	5
Nipple histologically involved (%)	12·2	8	30·2	50	16·5	23·4	25	28·6	31	16
Invasive tumour (%)	—	—	14·7	22·5	13·7	—	15·9	—	5·6	13
Non-invasive tumour (%)	—	—	15·5	27·5	2·8	—	9·1	—	25·4	3
Correlated with										
Clinical appearance	Yes	Yes	No	No	Yes	Yes	No	—	No	—
Tumour size	Yes	—	Yes	No	Yes	Yes	Yes	Yes	Yes	No
Tumour site	Yes	—	Yes	No	—	Yes	—	—	Yes	Yes
Lymph node status	Yes	No	Yes	—	Yes	Yes	Yes	Yes	Yes	Yes
Differentiation	Yes	Yes	Yes	—	—	—	—	—	—	—

—, Information not available

that a clinically normal nipple may often contain unsuspected neoplastic tissue. Close examination of these studies indicate that the majority of clinically normal but histologically positive nipples can be identified on the basis of tumour site, tumour size, tumour differentiation and axillary lymph node status. The findings in our retrospective series agree with these findings. In particular, involvement of the nipple was related to centrally situated tumours ($P < 0{\cdot}000001$) and to those with four or more positive axillary nodes ($P < 0{\cdot}01$). The relatively low overall incidence of nipple involvement (16 per cent) is a direct reflection of the fact that only two sections of the nipple-bearing area were examined. There appears to be little doubt that the more exacting the search for nipple involvement, the higher the positive yield will be. Thus Andersen and Pallesen, by examining 14 blocks, found the presence of tumour in 50 per cent of 40 cases. However in many of these additional cases only non-invasive tumour was found[13]; moreover the lack of relationship between tumour site and nipple involvement may well be because their central zone included only a 1 cm margin of periareolar breast tissue. In the present series nipple preservation was considered only when the tumour edge lay at least 2 cm from the edge of the areola. As a further safeguard it was deemed essential that a frozen section of the sub-nipple area was negative before nipple preservation could be carried out. This would mitigate against preserving nipples with infiltration into the third level described by Andersen and Pallesen[13].

The clearcut results of our retrospective study appeared to justify an assessment of the safety of nipple preservation in a prospective manner. There are no such other studies, presumably because of two areas of disquiet. Firstly, there are anecdotal case reports of tumour growing in the thighs of patients who have had 'nipple banking' as a preliminary to later reconstruction[7-10]. According to the criteria outlined above, these cases were entirely unsuitable for nipple preservation by virtue of having tumour present in the sub-nipple area or more than 4 positive axillary nodes. As there is a small risk that a retained nipple may harbour premalignant or invasive tumour the practice of 'nipple-banking' on the thigh must be condemned because hitherto unexposed lymphatic channels may be contaminated. In contrast, if there is recurrence in a nipple preserved on the breast flap then no new channels are exposed to tumour infiltration.

The second objection to nipple preservation stems from the widely held belief that the lymphatic drainage of the breast passes to the sub-areolar plexus of Sappey before distribution to the axilla or internal mammary chain. This theory was discredited by Turner-Warwick in 1958, who showed, using vital staining techniques and autoradiography, that the majority of lymphatic channels accompany blood vessels and permeate through the substance of the breast without any significant relay to the nipple area[2]. Indeed a review of Sappey's original paper reveals that his studies were carried out on the lactating rather than the resting breast.

Several significant findings have emerged from the prospective study. In all 20 instances when the nipple was preserved, the sub-nipple area was histologically tumour-free. However, nipple recurrence occurred in one patient in whom the recurrent tumour was intraductal and non-invasive. It is uncertain whether such changes affect the survival of an individual patient, but this case demonstrates the potential for recurrence within major duct remnants identical with the small risk following subcutaneous mastectomy. Such an occurrence after breast conservation has recently been reported by Plowman *et al.*[20]. This risk will be all but eliminated if deskeletonization of the nipple is carried out as has been suggested by Randall, Dabb and Loc[21]. Apart from this case the incidence of flap recurrence was similar in both groups of patients. The immediate advantages of nipple preservation were particularly noted in patients with eccentrically placed tumours where retention of the nipple on the skin flap aided skin closure. Four patients who had nipple preservation suffered from partial or full thickness loss of the nipple itself. This resulted from cutting the skin flaps too close to the undersurface of the nipple and areola, and all four cases occurred early in our series.

It is possible to construct a new areola and nipple from the contralateral areola, from thigh or vulval skin, or even from haemorrhoidal tissue[3-5]. These techniques produce a cosmetic result inferior to that of the real nipple itself.

An alternative method of nipple preservation is by subcutaneous mastectomy[6]. Although this technique has not been associated with any excess nipple or flap recurrence, it may not permit an accurate assessment of the sub-nipple area[22]. Another potential problem following subcutaneous mastectomy was highlighted by Wertheim and Ozzello who noted that unsuspected skin involvement distant to the tumour bearing area was present in 11·3 per cent of 1000 mastectomy specimens[15].

It is concluded that: extension of tumour into the nipple is rare in small, peripheral, node negative tumours; in such patients, providing the sub-nipple area is tumour-free, the nipple can be preserved; and this technique facilitates skin closure, markedly improves the cosmetic result of subsequent breast reconstruction, and does not appear to increase the risk of flap recurrence.

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Stitch granulomata after thyroid surgery

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Foreign body granulomata are known to follow the use of silk suture material deep to the skin. This complication was noted to occur after thyroid surgery and a retrospective survey was carried out to assess both the incidence and morbidity of this problem. The change from the use of silk to synthetic absorbable material for all purposes deep to the skin was then assessed.

Materials and methods

The records of a single surgical firm with a special interest in thyroid surgery were examined. Between January 1977 and December 1982 silk was used for all ligatures and sutures; from January 1983 to December 1984 synthetic absorbable material (Vicryl or Dexon) was employed. A smaller group of patients found from Welsh Office records had granulomas due to operations performed before 1977; this provided information regarding late presentation of the problem.

Results

Incidence

It will be seen from *Table 1* that no granulomata occurred after discarding silk. Before this time there were 40 cases of granulomata in 526 operations; an incidence of 8 per cent. No other complications occurred as a result of changing from silk to absorbable material.

Time to presentation

Eighty per cent of granulomata presented within 2 years of the original operation. In the unselected group there were four instances in which the initial symptom or sign of the granuloma was over 4 years from the time of operation.

Relationship to thyroid pathology and surgery

Granulomata were more frequent after surgery for Graves' disease – an incidence of 13 per cent compared with 8 per cent overall; likewise an increased frequency was noted with follicular adenoma (12 per cent) (*Figure 1*). Granulomata were also more frequent following subtotal procedures where a thyroid remnant was sutured to the trachea to obtain haemostasis compared with total procedures (incidences of 9 per cent and 3 per cent respectively).

Table 1 *Annual incidence of granulomata*

Year	Total operations	Granulomata	Incidence (%)
Silk in use			
1977	116	3	2·5
1978	80	5	6
1979	63	4	6·5
1980	103	12	12
1981	85	9	10·5
1982	79	7	9
Absorbable suture in use			
1983	92	0	0
1984	91	0	0

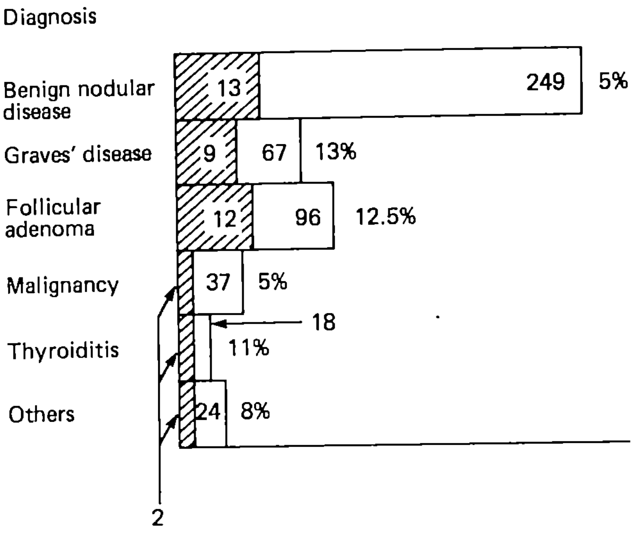

Figure 1 *Percentage incidence of granulomata. Numbers show number of patients developing granulomata (▨) out of total (☐) number of patients and percentage*

Morbidity

Considerable morbidity resulted from silk granulomata. In 75 per cent of patients the time from presentation to cessation of symptoms was over 6 months. One or more operations were required in 65 per cent and in 50 per cent multiple episodes of discharge or operation were required. Surgery was required in 26 patients who underwent a total of 36 procedures.

Discussion

Experimental work has shown the tissue reaction to absorbable suture material to subside in around 60 days. By contrast silk causes a greater inflammatory reaction which persists[1,2]. The high incidence of granulomata should not therefore be unexpected but the problem has received little attention in reviews of the complications of thyroid surgery[3]. The complication has been found in other fields: neurosurgeons have noted the problem and by avoiding silk were able to prevent granulomata[4]. The increased incidence in sub-total procedures is probably because more silk would have been used as ligature or suture to obtain haemostasis. This would also have been the case in Graves' goitres but there is no obvious reason why those with follicular adenomas should have been so affected.

In conclusion, the use of silk in the neck during thyroid surgery causes significant morbidity which can be prevented by using absorbable sutures. Since these materials are not themselves associated with any complication the use of silk in the neck should be abandoned.

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Br. J. Surg. 1987, Vol. 74, January, 63

Does intercostal blockade improve patient comfort after cholecystectomy?

W. B. Ross, J. H. Tweedie, Y. P. Leong, A. Wyman and B. M. Smithers

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The aim of this trial was to investigate the effect of a single intercostal blockade on the patient's comfort during the early postoperative phase.

Patients and methods

A total of 107 patients were entered in the trial, but 15 patients were later withdrawn. All patients signed an informed consent form.

The methods of pre-medication and induction and anaesthesia were not standardized. All cholecystectomies were performed through either a transverse upper abdominal or an oblique subcostal incision. An operative cholangiogram was performed and patients with choledocholithiasis were withdrawn from the trial. A plastic tube drain was used in every case.

At the end of the operation, patients were randomly allocated to one of two groups. Group 1 had an intercostal block combined with papaveretum (ICB + P) for postoperative analgesia. Group 2 did not have intercostal blockade and received papaveretum (P) only. Intercostal blockade was performed, by the authors, using the method described by Nunn and Slavin[1]. Seven nerves (T_5–T_{11}) were blocked, 3 ml 0·5 per cent bupivacaine (containing 1:200 000 adrenaline) were injected in each intercostal space. A long Elastoplast dressing was applied over the left ribs posteriorly in all patients. This kept patients and nurses unaware of whether a blockade had or had not been performed. Nursing staff were asked to administer papaveretum when requested by the patients who had been instructed to request pain relief when they required it, rather than wait to be asked.

On return to the ward, the patients were restricted to 30 ml water per hour orally. The intravenous infusion was reduced to 500 ml per 8 hours at midnight after surgery. The next morning, all patients were encouraged to take oral fluids. Metoclopramide was prescribed for nausea and vomiting as required. Patients received a standard physiotherapy regime. Patients had been operated on during morning and afternoon lists, but were visited twice daily, at 8 a.m. and 8 p.m. approximately, by one of the authors in order to assess pain and nausea (using linear analogue scales) and also to examine the chest for atelectasis. Patients were reviewed 4 weeks after discharge. Statistical analysis were performed using Student's *t* test and χ^2 tests. The Mann–Whitney *U* test was applied to compare non-parametric data.

Results

Both groups were comparable in respect of age, sex, weight, height, incidence of smoking and duration of the operation. There was no significant difference between the two complication rates. The definition of 'chest infection' was taken to be the presence of atelectasis and pyrexia or production of purulent sputum. Chest infections were treated with ampicillin and physiotherapy. In Group 1 (ICB + P) 10 (24 per cent) patients developed chest infections compared with 8 (16 per cent) in Group 2 (P), this was not significant. In Group 1 (ICB + P) there was a higher incidence of atelectasis (38 *versus* 34 per cent), but this was not significant. One patient developed a small pneumothorax after ICB.

The mean interval between the end of the operation and administration of the first dose of analgesic was significantly longer in Group 1 (ICB + P) than in Group 2 (6·46 (s.e.m. = 1·19) *versus* 3·25 (s.e.m. = 0·54) h; $P < 0·005$).

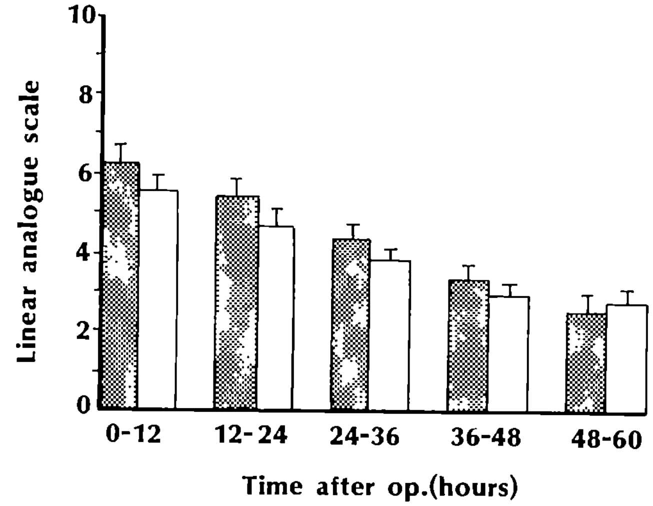

Figure 1 *Degree of pain. Mean score ± s.e.m.* ▨, *intercostal block and papaveretum;* □, *papaveretum alone*

Table 1 *Nausea scores: linear analogue scale, 0–10*

Time after operation (h)	0–12	12–24	24–36	36–48	48–60
ICB+ papaveretum	2·05 (0·50)	1·71 (0·41)	1·35 (0·42)	0·75 (0·30)	2·28 (0·35)
Papaveretum alone	2·07 (0·46)	1·71 (0·44)	1·20 (0·36)	0·35 (0·15)	0·32 (0·08)

Values are mean ± s.e.m.

This suggests that the intercostal blockade was an effective analgesic. However, there was no difference (ICB + P *versus* P), between the consumption of papaveretum (0·77 (s.e.m. = 0·19) *versus* 0·71 (s.e.m. = 0·06) mg/kg body weight) and metoclopramide (0·24 (s.e.m. = 0·03) *versus* 0·22 (s.e.m. = 0·03) mg/kg body weight). Both groups had similar incidences of postoperative vomiting, with an overall incidence of 31·5 per cent. Both groups experienced similar degrees of pain (*Figure 1*) and durations of nausea (*Table 1*).

Discussion

Murphy suggested continuous intercostal nerve blockade by insertion of a single extradural catheter into an appropriate intercostal space and administering local anaesthetic via this 'on demand'[2]. This would appear to be an improvement on the technique of multiple intercostal blocks reported by Moore[3].

The overall incidence of vomiting (31·5 per cent) is high. This is probably related to the observations that postoperative vomiting is more prevalent among females and the obese[4]. These factors were also prevalent in our study.

The results of this study question the effectiveness of intercostal block in the management of pain after cholecystectomy. There is in addition a small, but not neglible, risk of pneumothorax. We conclude that it does not reduce the need for narcotic analgesics and does not improve the patient's comfort.

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Rate of bacterial recolonization of the skin after preparation: four methods compared

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Previous studies have shown that recolonization of the skin surface occurs after disinfection[1] but there has been little investigation of this phenomenon. We have studied the rate of recolonization of the skin surface after preparation by the methods in most frequent use and under plastic adhesive drapes with and without slow-release iodophor.

Methods

Fifteen volunteers lay supine for 3 hours in an empty operating theatre. Five rectangular areas were marked on the abdomen of each volunteer and a different antiseptic preparation was applied to four of the five areas. These were: 3 min painting with chlorhexidine in 70 per cent alcohol; 3 min painting with povidone–iodine in 70 per cent alcohol; 1 min painting with 70 per cent isopropyl alcohol and application of a plastic adhesive drape ('Opsite', Smith and Nephew Ltd); and 1 min painting with 70 per cent isopropyl alcohol and application of a plastic adhesive drape containing slow-release iodophor ('Ioban drape' 3M Health Care). The fifth area was used as a control.

Samples were taken from a different part of each area after 5, 30, 60 and 180 min, using Rodac contact sampling plates containing oxoid columbia agar with 10 per cent horse blood, 1 per cent Tween 80, 0·3 per cent azolectin and 0·3 per cent sodium thiosulphate. After aerobic incubation the bacterial count on each plate was recorded.

Results

The control values showed a truncated log normal distribution. Initially the methods were equally effective in removing bacteria, each showing a median bacterial reduction of 100 per cent. Recolonization of the skin surface occurred progressively. The distributions of successive samples from prepared areas showed a progressive increase toward the distribution of control values. The rate of recolonization depended upon the preparation used. Differences were apparent at 30 and 60 min and increased at 180 min (*Figure 1*). Recolonization was less after preparation with the slow-release iodophor drape then with the other methods. This difference was significant at 60 min ($P = 0{\cdot}05$, Friedman test) and highly significant ($P = 0{\cdot}01$, Friedman test) at 180 min.

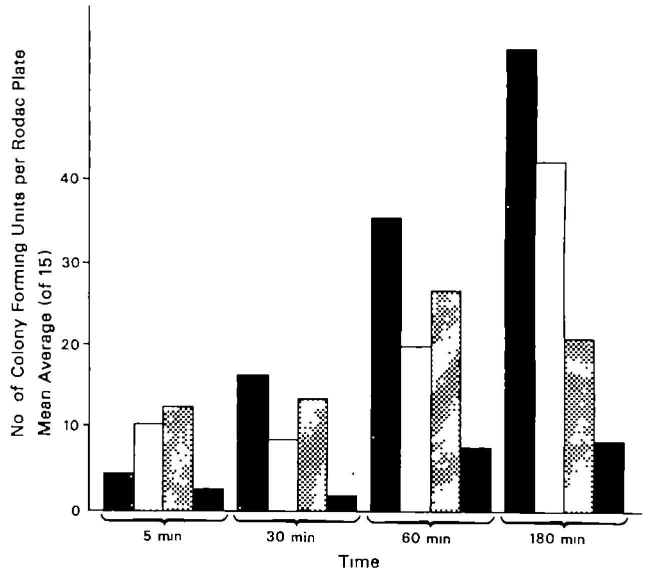

Figure 1 *Mean average results of the four different preparatory methods at each of the sampling times: ▨, chlorhexidine in alcohol; ☐, povidone–iodine in alcohol; ☐, alcohol and adhesive drape; ■, alcohol and iodophor drape*

Discussion

It has been shown that seeded organisms are removed by antiseptics and do not re-establish themselves[2]. The behaviour of normal flora may be more relevant to the maintenance of asepsis. Normal skin bacteria can only be reduced to a certain level after which re-emergence from deeper layers, and recolonization of the surface occurs.

The contact-culture method employed[3] samples organisms on the skin surface which could be mechanically transmitted into a wound. This sampling method is simple and provides a basis for comparing forms of disinfection.

All four methods of skin preparation were effective in removing bacteria from the skin surface. Thereafter recolonization proceeded at different rates. Within the duration of the study the slow-release iodophor drape was more effective than the other regimens in delaying bacterial recolonization. Further studies are indicated to determine whether any clinical benefit arises from the apparent superiority of this method of pre-operative skin preparation.

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New silicone rubber mat: a simple aid for laparotomy wound closure

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The closure of the musculo-aponeurotic layer of abdominal laparotomy wounds demands consistent technical excellence to avoid the dangers and discomfort of a major wound dehiscence or incisional hernia. In 1947, McNeill Love[1] described the use of rectangular rubber dams made from the inner tubes of car tyres to aid resuture of the burst abdomen at the Royal Northern Hospital, London. A tape was attached to the device to retrieve it from the wound. The following device (Lapromat®: Clinimed Ltd, Cavell House, Amersham Hill, High Wycombe, Bucks HP13 6NZ, UK) has been developed to provide additional assistance during laparotomy wound closure by protecting the underlying viscera and effectively defining the layers of the abdominal wall during layered or mass closure.

The device is made in three sizes of silicone elastomer rendered radio-opaque with 2 per cent barium sulphate (British Standard B.S. 5736). The flat flexible mats are manufactured from a 2 mm thick sheet in the form of a biconvex or elliptical shape. This shape was chosen because tissue elasticity dictates that wounds of the body cavities assume a biconvex shape along their long axis. The mat has an integral elongated tail-like extension or handle to avoid the need for tapes which could cut out through the silicone during removal (*Figure 1*). Once the viscera are replaced, the appropriate size of mat can be inserted between the parietal peritoneum and the underlying organs where it effectively prevents the prolapse of intestine into the wound. The tail extension enables the whole wound to be protected by the mat and it can be reflected on itself and secured by an artery forcep (*Figure 2*). The peritoneum at the inferior end of the wound should be secured with an artery forcep to facilitate the final stage of the closure. For long wounds, tissue holding forceps can be used to approximate the mid-point of the wound whilst the initial sutures are inserted. The wound can be sutured over the mat until one inch or less remains to be closed. By pulling the tail section, the device can then be gently and slowly withdrawn allowing placement of the final sutures.

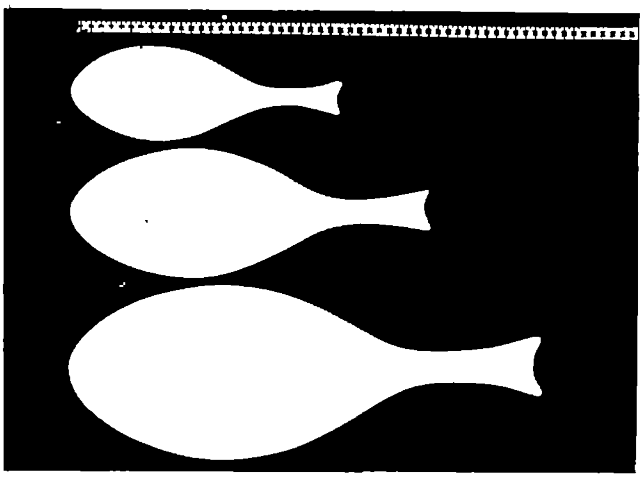

Figure 1 *Three sizes of the silicone rubber abdominal wound closure mat*

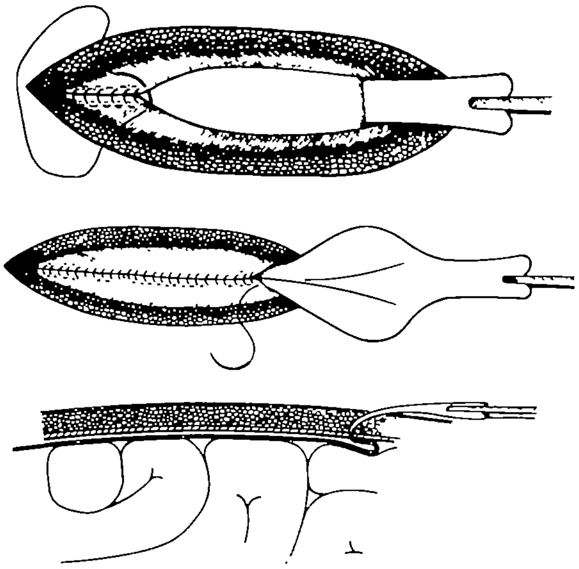

Figure 2 *Diagrams to illustrate closure of the wound with the mat in place during wound closure, removal of the device and the position of the silicone membrane in longitudinal section*

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Br. J. Surg. 1987, Vol. 74, January, 66

New general purpose rectal biopsy forceps

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Rectal biopsy is a frequently performed procedure in a gastroenterology clinic. New patients presenting with diarrhoea or those with known inflammatory bowel disease will often require biopsy. Biopsy will facilitate making the distinction between ulcerative colitis and Crohn's disease and sampling the submucosa will be of further assistance in this respect. Tissue obtained with the widely used Patterson forceps will include the submucosa in only one-third of biopsies[1]. This study was undertaken to assess new rectal biopsy forceps for their use in a general gastroenterology clinic.

Methods

The instrument

The shaft of the rectal biopsy forceps is rigid and is 40 cm in length. The jaws are cup-shaped and sharp (*Figure 1*) with a diameter of 6 mm and a depth of 3 mm. The jaws are similar to those of the Brock's bronchoscopy forceps (diameter 4 mm, depth 2 mm) but larger in size. The jaws are operated by a detachable universal handle.

The instrument is passed along a rigid sigmoidoscope and the biopsy is obtained by pressing the opened jaws into the mucosa, closing the jaws firmly and rotating the forceps until the tissue separates.

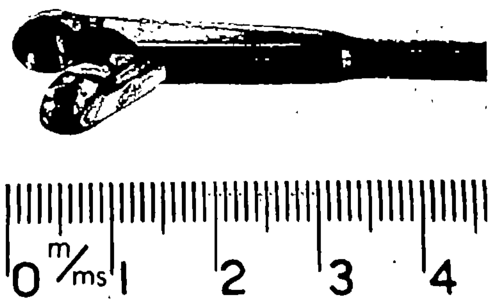

Figure 1 *Jaws of rectal biopsy forceps*

Table 1 *Histological assessment of 50 consecutive rectal biopsies*

Maximum depth of biopsy	Present study	Study by Preston *et al.*[1] St. Mark's forceps	 Patterson forceps
Mucosa	0	16	10
Muscularis mucosae	14	67	41
Submucosa	74	10	33
Muscularis propria	12	0	3
Inadequate for assessment	0	7	13

Values are percentages

Assessment

Biopsies were taken from 50 consecutive patients attending a general gastroenterology clinic. Each sample was mounted on cellulose acetate paper. Histological interpretation was greatly facilitated by the careful orientation of the biopsy on the cellulose acetate paper before formalin fixation. Histopathological assessment was performed by the same person (J.B.S.) noting the maximum depth of each biopsy and its adequacy for histological assessment.

Results

The histological diagnoses in the 50 patients were as follows: 35 normal, 11 ulcerative colitis, 2 Crohn's disease, 2 melanosis coli. The majority of the patients with a histologically normal rectal biopsy had irritable bowel syndrome. The submucosa was sampled in 86 per cent of biopsies. No biopsy sampled only mucosa and the depth of sampling was limited to the muscularis mucosae in only 14 per cent. The maximum depth of tissue sampled in the biopsies in this study is compared with those obtained using the new St. Mark's forceps and the Patterson forceps in a similar study[1] in *Table 1*.

One patient with irritable bowel syndrome reported rectal bleeding after biopsy but did not require any active treatment. A second patient – a 15-year-old boy being investigated for abdominal pain – developed pain and fever after the procedure which settled on conservative management without a definite diagnosis being reached.

Discussion

The new rectal biopsy forceps always provided a biopsy suitable for histological assessment which is in contrast to the results obtained with the widely used Patterson forceps and the St. Mark's forceps which failed to do so in 13 per cent and 7 per cent of biopsies respectively[1]. Additionally, these new forceps provided a much greater depth of tissue sampling which may be of particular help in distinguishing between ulcerative colitis and Crohn's disease. The St. Mark's forceps were designed to sample the mucosa only and this is reflected in the inclusion of submucosa in only 10 per cent of rectal biopsies obtained with it[1]. The Patterson forceps were, however, designed to obtain deeper samples, but only 36 per cent of rectal biopsies included the submucosa[1], whereas the new rectal biopsy forceps sampled the submucosa in 86 per cent of biopsies.

There was only one patient in this study who suffered a definite complication, that of rectal bleeding. This is a comparable incidence to that described in other studies[1,2].

The forceps described in this study are easy to use, safe and provide a reliable rectal biopsy suitable for histological assessment with a good depth of tissue sampling. They are inexpensive – price £120 excluding VAT – and can be recommended as suitable for use in a general gastroenterology clinic.

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The forceps are manufactured and distributed by Abbey Surgical Instruments (Surrey) Ltd, 31 Wates Way, Mitcham, Surrey, CR4 4HR, UK

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Case reports

Br. J. Surg. 1987, Vol. 74, January, 67–68

Peripheral false aneurysms in Behcet's disease

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In 1937 Behcet described a syndrome characterized by recurrent orogenital ulcers associated with relapsing iritis[1]. Today it is recognized as a chronic multisystem disease with a relapsing course. It affects diverse racial groups, being reported originally in Turkey[1], in Japan[2], Australia[3], and subsequently in Britain[4], China[5] and the Middle East[6].

The aetiology remains uncertain. A viral factor may be involved[7]. The diagnosis is based on the manifestation of clinical criteria consistent with Behcet's disease and the presence of HLA-B_5 antigen. Up to 24 per cent of patients with Behcet's disease have been reported to suffer at some time from vascular complications[8], thrombophlebitis being the most common. Budd–Chiari syndrome has also been reported[9]. The arterial system is rarely affected. Complications which have been reported are vasculitis leading to arterial thrombosis[10–12], and aneurysms of the aorta and less commonly of peripheral arteries. We found only one case of spontaneous false aneurysm formation[4] amongst the six reported cases of peripheral aneurysm in patients with Behcet's disease (*Table 1*). We describe a second such case.

Case report

A 28-year-old Israeli born Jewish man of Iraqi extraction presented with a mass in the right groin which he had first noticed 2 months previously. One week before admission the swelling had started to expand and become painful. There was no history of trauma, or needle puncture in the region.

Behcet's disease had been diagnosed some years previously, following the appearance of episodes of thrombophlebitis, orogenital ulcers, uveitis, epididymitis, erythema nodosum, arthritis and headache. HLA typing had been positive for B_5 and B_{35}.

On examination on admission a pulsatile mass 3 × 3 × 4·5 cm was present in the right groin. All peripheral pulses were present and normal on Doppler studies. Ultrasound examination confirmed an aneurysm of the right common femoral artery and revealed no intra-abdominal aneurysms.

The right groin was explored and a false aneurysm of the common femoral artery was found arising from a defect in its posterolateral wall. The defective portion of the common femoral artery was resected and replaced by an 8 mm GORE-TEX* interposition graft. Despite a postoperative fever no infective focus was found and the wound healed primarily. Pathological examination of the excised artery showed no specific changes.

Table 1 *Reported cases of peripheral aneurysm*

Author	Artery	Type of aneurysm	Pathogenesis
Jenkins[4]	Femoral	False	Spontaneous
Jenkins[4]	Femoral	True	Spontaneous
Kingston[6]	Femoral	False	Arteriography
Kingston[6]	Brachial	False	Arterial–puncture
Enoch[13]	Popliteal	True	Spontaneous
Crick[15]	Femoral	True	Spontaneous

Three months later, the patient was readmitted following the sudden re-appearance of a painful mass in the right groin. On examination there was a tender pulsatile 3 × 3 × 4 cm mass at the operative site. Ultrasound and angiographic studies (*Figure 1*) confirmed a false aneurysm at the site of the graft. Re-exploration of the groin was performed and a false aneurysm at the distal anastomosis was found. Owing to scarring and degeneration at the bifurcation of the common femoral artery, reanastomosis could not be performed and the bifurcation was therefore oversewn and an above-knee femoropopliteal bypass performed, again using an 8 mm GORE-TEX graft. Cultures taken from the operative site were all sterile. Postoperatively the patient again had a fever up to 39°C. No focus of infection was located and the temperature subsided by the fourth postoperative day.

One month later the patient presented with a painless mass in the right thigh above the knee. Ultrasound studies and angiography (*Figure 2*) confirmed a false aneurysm at the site of the distal anastomosis. At operation the aneurysmal sac was resected. GORE-TEX graft was re-anastomosed to the popliteal artery. Immediately after this procedure, the graft thrombosed but Fogarty thrombectomy was successful. Once again the patient had a postoperative febrile period. Cultures taken from the anastomotic site at operation were all sterile. On the tenth postoperative day a wound infection developed, cultures growing coagulase positive haemolytic staphylococcus. The wound healed after drainage and appropriate antibiotic therapy. The patient was discharged with normal pedal pulses.

One month later the patient was again admitted complaining of the sudden appearance of intermittent claudication of the right calf at 40 m. No distal pulses could be palpated in the leg. Angiography confirmed obstruction of the femoropopliteal graft. No further operation was performed and the patient has since been followed for 10 months without deterioration in the claudication, or the appearance of additional aneurysms.

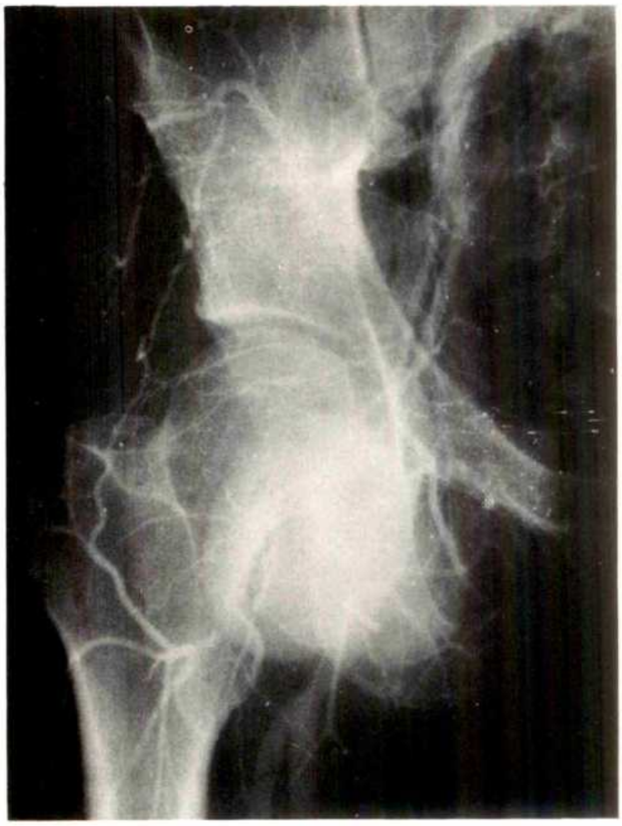

Figure 1 *Angiographic study defining a false aneurysm at the distal anastomosis of the 8 mm GORE-TEX interposition graft*

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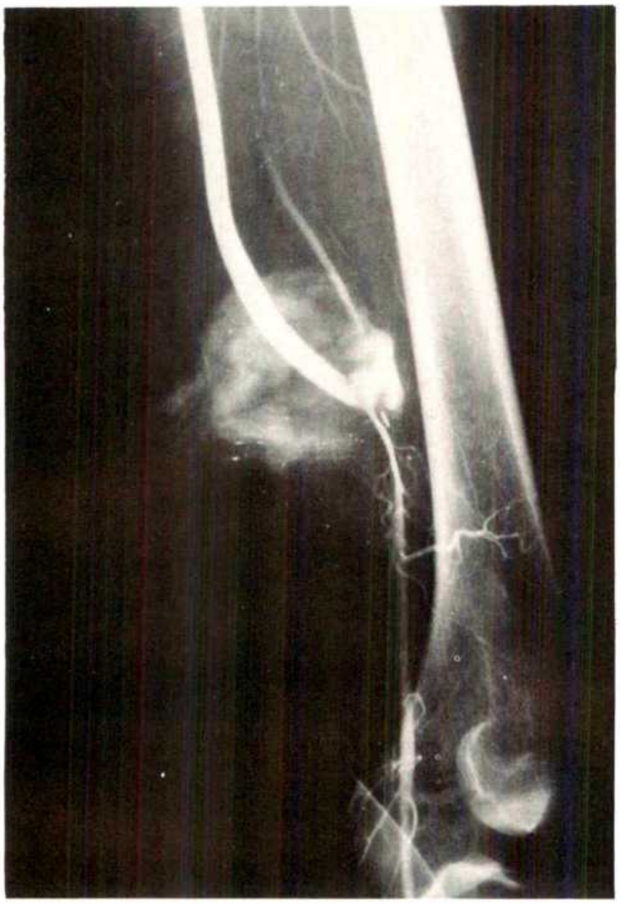

Figure 2 *Angiographic study demonstrating the false aneurysm at the distal anastomosis of the femoro-popliteal GORE-TEX graft*

Discussion

The most common site of peripheral aneurysm in Behcet's disease in the few cases described is the common femoral artery. Of the spontaneous aneurysms, only one was false[4]. In the case described by us a defect was found in the posterior wall of the common femoral artery, communicating with a posterolateral false aneurysm. The cause of the aneurysm may be the gradual weakening the arterial wall secondary to obliterative endarteritis of the vasa vasorum as described by Enoch[13].

Arterial complications in Behcet's disease present difficult surgical problems. Repairs, whether using autogenous vein or synthetic graft, nearly always result in anastomotic false aneurysm formation[4,6,13]. Because of the past history of superficial thrombophlebitis involving the leg veins, the use of a synthetic graft was prefered to autogenous vein. However this choice did not prove satisfactory. Another complication of surgery is graft thrombosis. In the case described by Enoch[13] in one popliteal artery graft thrombosis occurred and in the other a recurrent aneurysm developed at the site of anastomosis. Prolonged postoperative pyrexia and delayed wound healing may occur as a reflection of the generalized manifestations of Behcet's disease.

We describe a further case of spontaneous false aneurysm occurring in a young patient with Behcet's disease, showing typical complications following surgery.

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69–70

Spontaneous regression of pulmonary metastases from renal adenocarcinoma before nephrectomy

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The rare phenomenon of spontaneous regression of metastatic carcinoma is reported most commonly in association with renal adenocarcinoma[1]. In 61 of the 68 reported cases[2,3] the lungs have been the site of metastatic disease, and in only six of these cases has regression been reported before treatment[4–10]. We report a further such case, and discuss the associated reversible hepatic dysfunction.

Case report

A 57-year-old man was referred to hospital in June 1983 with intermittent claudication, hypertension and proteinuria. Clinical examination demonstrated hepatomegaly and chest X-ray showed appearances consistent with pulmonary metastases (*Figure 1a*). The patient had no history of chest disease or exposure to tuberculosis. Isotope liver scan confirmed hepatomegaly and demonstrated irregular uptake suggestive, but not diagnostic, of hepatic metastases. Laboratory tests revealed a haemoglobin of 10·4 g/dl, white cell count of 12·5 × 10^9/l, ESR 125 mm/h, albumin 21 g/l, globulin 46 g/l, alkaline phosphatase 343 units/l (normal: 100–280 units/l) with normal bilirubin and transaminases. Intravenous urography showed downward displacement of the right kidney due possibly to hepatomegaly. CT examination revealed that the right kidney was displaced by a posterior renal mass (*Figure 2*) but no liver metastases or ascites were shown. A CT scan of thorax was not carried out. A second chest X-ray in November 1983 showed spontaneous regression of the presumed pulmonary metastases (*Figure 1b*). Repeat laboratory investigations revealed haemoglobin of 16 g/dl, ESR 12 mm/h, white cell count 11 × 10^9/l, albumin 29 g/l and the liver function tests had returned to normal. Following arteriography, a right nephrectomy was performed later that month, when a renal adenocarcinoma with very extensive necrosis was removed.

On routine investigation in May 1986, in the absence of any clinical symptoms, chest X-ray showed a single round opacity in the left mid-zone suggesting recurrent metastatic disease. Liver scanning using isotope and ultrasound techniques demonstrated no parenchymal abnormality.

Discussion

Spontaneous regression of a tumour denotes partial or complete disappearance in the absence of treatment or in the presence of therapy which is inadequate to exert a significant influence; it is not necessarily synonymous with cure. The first report of regression of pulmonary metastasis from renal cell adenocarcinoma came from Bumpus in 1928[10]. Review of this subject demonstrates that spontaneous regression of metastatic renal adenocarcinoma can be anticipated in no more than 0·8 per cent of cases[11]. In the absence of treatment this phenomenon is far less likely, with only six reported cases in the literature. Spontaneous regression does not mean cure as almost 50 per cent of patients develop recurrent tumour[2].

An associated feature of the present case was reversible liver enlargement and hepatic dysfunction in the absence of liver metastases. This association with renal adenocarcinoma was first recognized in 1961[12], and is reported in up to 40 per cent of patients[13]. The histological features reported are non-specific reversible hepatitis characterized by Kupffer cell proliferation, mild hepatocellular degeneration and portal triaditis. This may have been the cause of the abnormalities on isotope liver scan in

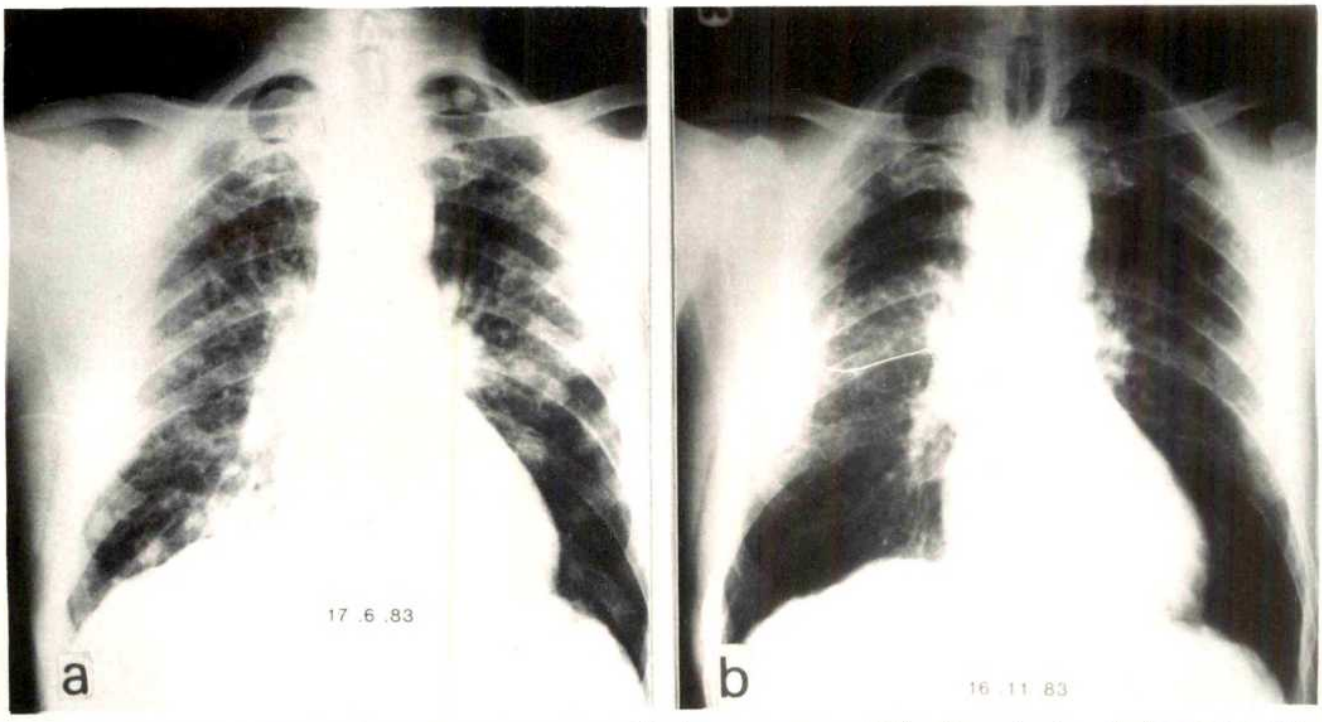

Figure 1 **a** *Chest X-ray on admission. The appearance is consistent with pulmonary metastases.* **b** *Chest X-ray after 5 months showing regression*

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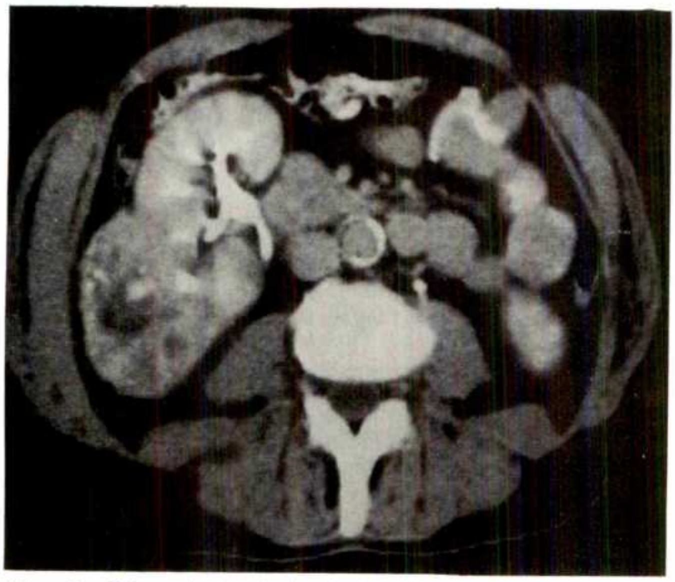

Figure 2 *CT scan showing displaced right kidney but no liver metastases or ascites*

our patient. The aetiology of reversible hepatic dysfunction is unknown and it has been described in association with a number of other gastrointestinal malignancies and with xanthogranulomatous pyelonephritis[13]. It may be no more than a non-specific consequence of chronic disease and this possibility should be borne in mind during management.

Acknowledgements

We would like to thank Mr J. M. O'Brien for his permission to report this case and Dr D. Tudway for carrying out the radiological investigations. Miss A. Yeoman typed the manuscript.

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Chylous ascites following aortic surgery

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Persistent lymph leak leading to ascites following aortic repair is extremely uncommon and chylous ascites following aortofemoral bypass has not previously been described. Conservative and operative management are discussed and a management protocol for this uncommon complication is proposed.

Case report

A 65-year-old man was admitted to hospital with a three-week history of gangrene of the left great toe. His past history included bilateral femoropopliteal bypasses and a right iliac endarterectomy performed several years earlier. He had an infection in the right groin following the right femoropopliteal bypass.

Angiography showed complete occlusion of the left common iliac artery, of both femoropopliteal bypasses and a severely diseased left profunda femoris artery. He underwent a left aortofemoral bypass graft and an extended left profundaplasty using an 8 mm knitted Cooley Dacron graft through a transabdominal approach and was discharged on the tenth postoperative day without complication and with a warm, pain-free foot.

Six weeks later he was readmitted with a 2 week history of left leg and abdominal swelling and weight loss. He was found to have ascites and underwent paracentesis of more than 7 litres of turbid fluid. On examination he was afebrile, displayed marked ascites and showed pitting oedema from the left ankle to the mid-thigh. There was no clinical evidence of venous thrombosis and he was not in congestive heart failure.

Laboratory data on admission showed a normal serum amylase, liver function tests, and coagulation profile. His haemoglobin on admission was 14·9 g/dl. Total serum proteins were 55 g/l (normal 52–84) and serum albumin was 27 g/l (normal 35–50). Ultrasound of the abdomen revealed a large amount of peritoneal fluid and a fluid collection in the left groin.

Paracentesis demonstrated cloudy yellow, odourless fluid which separate into layers on standing. Laboratory examination of the fluid revealed a total protein content of 21 g/l. Cytology showed no malignant cells and there were no bacteria. A diagnosis of chylous ascites was made. A lymphangiogram with an oil-based dye showed obstruction of lymph flow in the left iliac area, but no intra-abdominal leak of lymph. The patient was started on a low fat elemental diet by mouth with a medium chain triglyceride fatty supplement. His ascites continued to accumulate and his serum albumin to fall. On the twelfth hospital day an exploratory laparotomy was performed. Immediately before operation, methylene blue was injected into the web spaces of both feet. Seventeen litres of ascites were drained and a lymph leak was noted in the area of the ligament of Treitz. This area was oversewn with Dexon sutures and an omental flap placed. No methylene blue dye was seen. Postoperatively he was started on total parenteral nutrition with cessation of oral feedings for four weeks. Oral feeding was started in the fifth week and he was discharged one week later with normal serum proteins, no ascites and in good health.

Discussion

Chylous ascites is a very rare complication of abdominal aortic surgery. Literature review has revealed only five previously reported cases all following abdominal aortic aneurysm repair[1–5]. This is the first case reported following aortofemoral bypass. Bradham *et al.*[1] in 1970 described chylous ascites which developed after abdominal aneurysm repair and which did not respond to conservative treatment. At operation, closure of multiple small fistulae was curative.

The subsequent four cases[2–5] are similar. Most patients presented 2–6 weeks after abdominal aortic aneurysm repair and the diagnosis was accomplished by paracentesis. Chylous ascites will separate into layers on standing, is odourless or may have the odour of digested food. The specific gravity is usually greater than 1·012, the fluid it is usually alkaline and sterile and contains >4 per cent total solids. An increased fat content from 4–40 g/l may give a positive Sudan III stain. Total protein content is at least half that of plasma[6].

Chylous ascites has also been reported following operations such as pancreaticoduodenectomy[7], truncal vagotomy[8], retroperitoneal lymphadenectomy[9,10] and Warren distal-splenorenal shunt[11–12]. It is aggravated by pre-existing liver disease[14,15]. No case in the recent literature has resulted in death.

The danger of prolonged intra-abdominal lymph leak is nutritional wasting secondary to excess protein loss and fat malabsorbtion. Meinke *et al.*[4] suggested that surgery be performed early with preliminary oral alimentation or parenteral hyperalimentation for nutritional support.

Our treatment protocol is as follows (see *Figure 1*). Paracentesis is performed for diagnosis and appropriate laboratory evaluation. A patient who is a good operative candidate and is nutritionally replete should have a lymphangiogram followed shortly by laparotomy to close the fistula.

Conventional lymphangiography by injection at the foot may not visualize the intra-abdominal lymph fistula and pre-operative feeding of cream containing a vital dye such as Sudan Black or intra-operative injection of a vital dye into the small bowel mesentery may be preferable[13,15–17]. A negative pre-operative lymphangiogram should not contraindicate surgical repair.

A patient who is a good operative candidate, but who is not nutritionally replete should have nutritional supplements (preferably hyperalimentation with or without elemental feeds) followed by operative repair once his status improves. A patient who is a poor operative risk and who is nutritionally replete should be treated conservatively with a low fat diet, supplemented with medium chain triglycerides, repeat paracentesis, diuretics and bed rest until their status improves sufficiently to permit laparotomy. Poor risk patients who are not nutritionally replete should be treated with hyperalimentation paracentesis as necessary, bed rest and diuretics until they will tolerate operation. Finally, those patients who fail to close their fistula despite operation or who cannot tolerate laparotomy become candidates for peritoneal–venous shunt, a procedure that has proved useful in several cases[17,18].

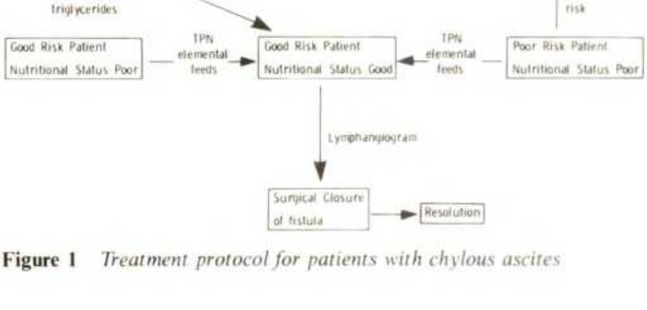

Figure 1 *Treatment protocol for patients with chylous ascites*

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Calculous disease of a primary vaginal hydrocele in an infant

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Calcium deposits have been described in the tunica vaginalis and on the surface of the testis in up to 20 per cent of hydroceles[1], but the occurrence of stones in a hydrocele sac has not been previously reported.

Case report

A 6-month-old male infant presented at the University of Calabar Teaching Hospital with a 2 month history of a swollen right scrotum. This swelling appeared spontaneously and had been increasing steadily in size. It was painless and the child had showed no symptoms referable to the swelling. It did not reduce in size when the child was recumbent nor did it increase in size on crying or straining during defaecation.

The child was the first baby of a working class young couple. He was delivered at term. Gestation and perinatal periods were uneventful and developmental milestones were normal.

Examination revealed an otherwise well looking and fit child with a tense non-tender brilliantly transilluminant swelling about the size of a hen's egg in the right sac. The right testis was not palpable and the swelling was confined to the scrotum. The swelling was irreducible and there were no bowel sounds on auscultation.

At operation the swelling was explored by an inguinal approach; no hernial sac was present. The hydrocele fluid whose volume was about 50 ml, was straw coloured. Nineteen greyish white stones were found within the hydrocele sac (*Figure 1*). The stones were firm but not hard and were about the size of peanuts. No organisms were cultured from the fluid and no parasites were isolated; on chemical analysis, the stones were composed of calcium oxalate, calcium phosphate and magnesium phosphate. Serum calcium was normal and there was no laboratory or clinical evidence of hyperparathyroidism.

Discussion

This patient is unique. The stones have all the features of primary urinary calculi. There were no bacteria, epithelial debris, fibrin or foreign body in the core and all were of uniform consistency and constituents. There was no evidence of communication between the tunica vaginalis and the urinary system or even the peritoneal cavity.

This is the first recorded case of primary stones of the tunica vaginalis.

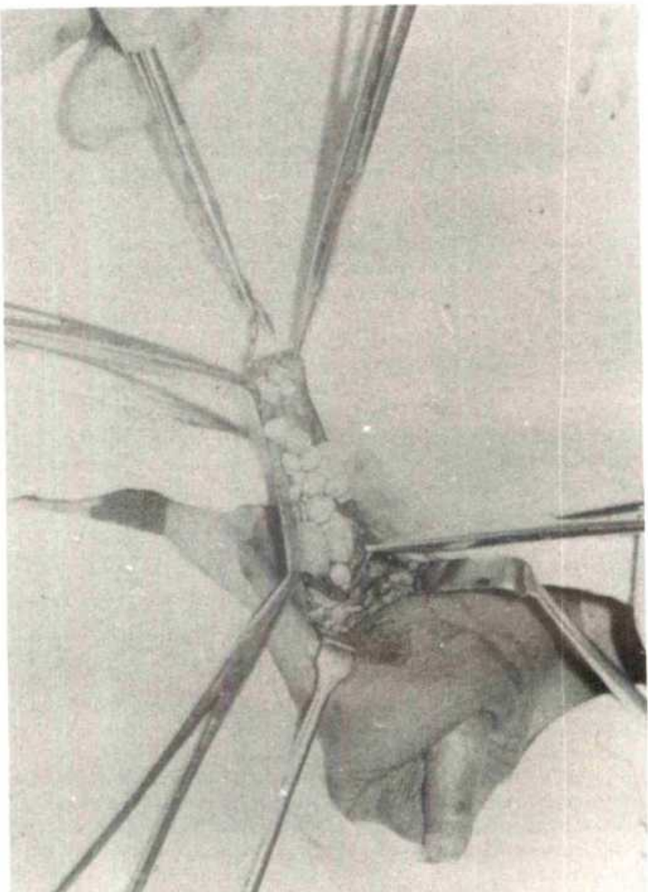

Figure 1 *Right vaginal hydrocele opened through a groin incision to expose 19 calculi surrounding the testis*

Acknowledgements

I wish to thank Professor I. O. K. Udozor and the staff of the Chemical Pathology and Microbiology Laboratories of the University of Calabar Teaching Hospital for analysing the stones.

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Paper accepted 30 July 1986

Br. J. Surg. 1987, Vol. 74, January,
73–74

Primary nerve tumours of the brachial plexus

P. J. Sell and J. C. Semple*

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Correspondence to: Mr P. J. Sell, 72 Holland Road, Sutton Coldfield, West Midlands, UK

Tumours of peripheral nerves are not common. They must be considered as a possible cause of swellings associated with pain or parathesiae in the upper limb or neck. In particular primary nerve tumours arising from the brachial plexus are rare. A review of 480 neurilemmomas outside the central nervous system revealed only 24 cases arising from the brachial plexus[1].

The problem of pre-operative diagnosis of nerve tumours in the hand and upper limb has been emphasized[2]. The medico-legal implications of surgery on an unsuspected neurilemmoma thought to be a lump in the neck have been mentioned in the Medical Defence Union Journal[3].

Case reports

Case 1

A 43-year-old oil rig worker complained of pain radiating down his right arm to the elbow. A small lump in the neck was thought to be a lymph node, although percussion of the lump caused a tingling sensation to the triceps region of the arm; there was no objective neurological deficit. On surgical exploration a tumour was found closely associated with nervous tissue; this was thought to be a neurofibroma and was incised and removed piecemeal. Postoperatively paralysis of the scapular muscles, deltoid and biceps became apparent, with EMG evidence of denervation of the upper trunk of the plexus. On surgical re-exploration the C_5 root was found to be involved in a mass of gliomatous tissue which was resected and a sural nerve graft was used to bridge the defect in C_5. At review 9 months later he had grade 2 strength in his deltoid muscle (Oxford scale) but was unable to abduct the shoulder. There was no muscle activity in biceps. Histology showed a neurilemmoma.

Case 2

A 28-year-old woman described pain in her right arm for 2 years, with 6 months parathesia over the lateral aspect of her upper arm, and hypoaesthesia over the thumb and index finger. Palpation of a tender nodule in the axilla produced pain radiating in the triceps region. Exploration revealed a typical well encapsulated 2 cm tumour which was easily enucleated from the lower roots of the brachial plexus. Postoperatively there was no neurological deficit. When reviewed 5 years later there was some slight tenderness at the site of the scar, but no neurological signs. Histology confirmed a neurilemmoma.

Case 3

A 50-year-old storeman presented with a 3 month history of general malaise, and pins and needles radiating down his right arm. His general practitioner had noted a lump in the neck. Though not recorded in the notes the patient volunteered weakness of his arm. The neck was explored and a lesion arising from the brachial plexus was found. Two days later the neck was re-explored and a 2·5 cm lesion was enucleated from the brachial plexus. Postoperatively the patient had hyperaesthesia, and 4 years later he is still attending a pain clinic for this. Histology confirmed a neurilemmoma.

Case 4

A 42-year-old right-handed motor mechanic noticed a tingling pain in his left elbow which radiated to the dorsum of his hand. Two months later he noted that pressure in his neck caused pain in this area. A swelling in the neck was found and this was thought to be a lymph node. Following surgical biopsy he developed numbness in the ring and middle fingers. Three weeks later the neck was re-explored and after incomplete excision of the lesion, he had total paralysis of his biceps muscle, and an increase in paraesthesia of the index, middle and ring fingers. The clinical picture was that of C_6 nerve root division. A CT scan of the neck was unhelpful in demonstrating the divided nerve root or the lump in the neck. Upon re-exploration a 5 × 4 cm lesion was found deep to the divided C_5 nerve root (*Figure 1*). The tumour was enucleated and removed. The C_5 nerve root was repaired. Histology confirmed a neurilemmoma.

Case 5

A 52-year-old manufacturing agent with a 1 month history of swelling in the left side of his neck had noticed pins and needles radiating into the lateral aspect of his forearm upon pressing on the neck lump. After biopsy he developed hypersensitivity over the lateral aspect of the forearm and weakness of elbow flexion. The biopsy was reported as a neurilemmoma. Three weeks later the neck was re-explored and with considerable difficulty the tumour measuring 4 × 3 cm was enucleated from the lateral cord of the brachial plexus. At review he had wasting of the upper arm and grade 4 power in the biceps. The hyperaesthesia had settled. Histology confirmed a neurilemmoma.

Case 6

A 14-year-old girl with neurofibromatosis was referred with a swelling in the root of her neck. When first seen there were no neurological symptoms or signs. She had had two previous operations where the lesion had been partially excised. Re-exploration was difficult because of the previous scarring; however, it was possible to enucleate a 14 × 8 cm neurofibroma. Her postoperative course was complicated by a haemorrhage requiring re-exploration. Surprisingly there was no neurological deficit postoperatively. The histological features were those of a neurofibroma.

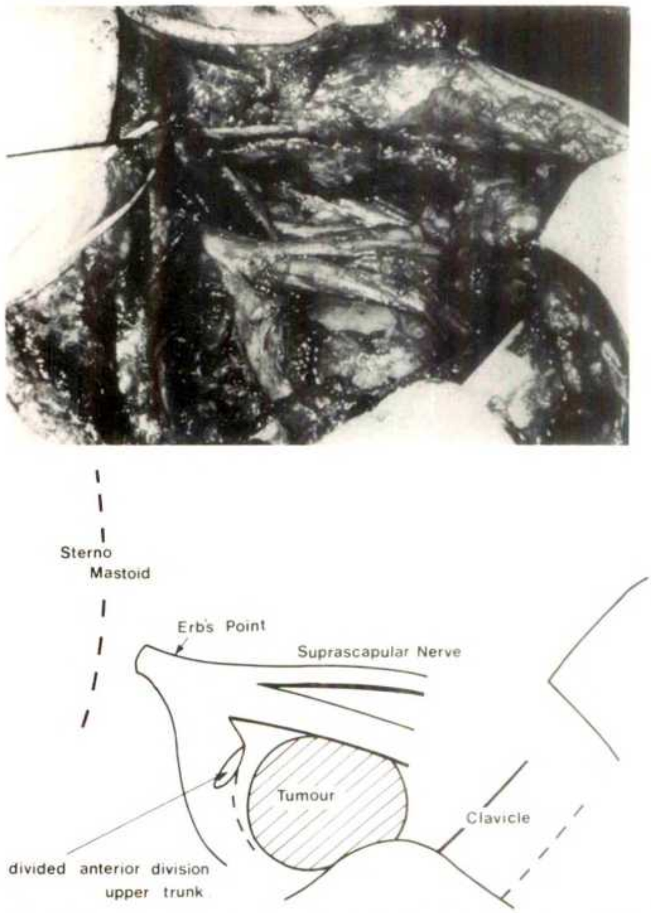

Figure 1 *Case 4. The 4 × 5 cm neurilemmoma is shown deep to the posterior division of the upper trunk of the brachial plexus. The divided anterior division of the upper trunk is demonstrated in the line drawing*

Discussion

Sir Herbert Seddon's comment on these tumours was, 'the trouble about these tumours is that they are just common enough to come within the experience of all surgeons, and are rare enough to cause embarrassment in diagnosis and treatment'[4].

The six cases reviewed consist of two females and four males, with an age range from 14 to 52 years, an average of 37 years. A total of 13 operations was performed to remove six benign lesions. The five neurilemmomas in this series all had characteristic diagnostic pre-operative neurological symptoms. It is unfortunate that initial exploration often resulted in the development of a neurological deficit. The ideal treatment for a tumour arising in a major nerve is enucleation, and an adequate exposure and expertise is required for this.

Nerve conduction and EMG studies might be of benefit pre-operatively in those cases with sensory symptoms, but all patients were seen after the initial exploration, which interferes with interpretation of the results except in the case of denervation. In one patient (case 1) EMG studies demonstrated denervation in the upper trunk of the brachial plexus which had been totally divided.

There are two types of benign primary tumour of peripheral nerve, the neurilemmoma and the neurofibroma[5]. Confusion arises from nomenclature; the neurilemmoma and the Schwannoma are different words for the same tumour[7]. The neurilemmoma arises from the Schwann cell, it is always encapsulated arising eccentrically from the nerve, and it can usually be removed without damage to the underlying nerve trunk. Once the plane of cleavage between the capsule and nerve fasicle has been found, enucleation is generally straight forward. Neurofibromata arise from the fibroblast, and may be solitary or multiple, occurring within the fasicle itself; excision leads to an inevitable neurological deficit.

The pathology of neurilemmoma is well documented and distinctive. Larger lesions are divided into compact solid areas that are relatively highly cellular, Antoni type A, and areas that are loose, reticular and less cellular, Antoni type B[7]. This makes a confident diagnosis possible. Malignant transformation of neurilemmoma does not occur, and there is no indication for risk-taking in difficult anatomic sites. If sub-total excision is clinically prudent the lesion seldom regains its pre-excision size, but persists as a static latent lesion[6].

In the differential diagnosis of lumps in the neck, neurilemmoma should be considered particularly when sensory symptoms or signs are evident. The clue to the diagnosis lies in the tingling that results when local pressure is applied.

Acknowledgements

Many thanks to the Medical Illustration Department, Western Infirmary Glasgow and to the secretaries of East Birmingham Hospital.

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Paper accepted 30 June 1986

Correspondence

FFP in pancreatitis

Sir

The recent paper by Goodman *et al.* (*Br J Surg* 1986; **73**: 796–8) demonstrates the interesting changes of serum antiprotease levels in acute pancreatitis. In view of the very small number of patients entered into the trial of fresh frozen plasma (three to FFP, two to colloid control) no conclusion can be drawn from their work regarding the possible therapeutic role of FFP in acute pancreatitis. Four of these five patients died and, although the authors do not state the timing of the deaths, a comparison between antiprotease levels in the two groups is difficult. They may have overstated the volume of FFP administered as three standard units of FFP represents a volume of approximately 700 ml rather than 1200 ml.

A multicentre trial co-ordinated in Leicester has been in progress since March 1985 in which patients with acute pancreatitis are randomized to receive either FFP (six units over 3 days) or colloid control as part of the intravenous fluid therapy. The major antiproteases are measured on days 1, 3 and 7.

To date 160 patients have been entered into the trial. No significant difference has been shown between the two groups in terms of clinical outcome (12 severe outcomes with 6 deaths in the FFP group, 19 severe outcomes with 8 deaths in the colloid control group). In both groups α_1 antiprotease levels were already elevated at diagnosis and rose significantly from day 1 to day 3 ($P<0\cdot0001$) remaining elevated at day 7. These findings correspond with those of Mr Goodman and confirm an acute phase response which is not influenced by the administration of FFP. α_2 macroglobulin levels were subnormal at diagnosis in both groups (as found by Mr Goodman) and fell significantly from day 1 to day 3 in the colloid control group ($P<0\cdot05$) whilst remaining substantially unaltered in the FFP group ($P=0\cdot91$, two-tailed Mann–Whitney ranking test).

The place for fresh frozen plasma in the therapy of acute pancreatitis has yet to be determined, but it appears that fresh frozen plasma can reduce the fall in serum α_2 macroglobulin levels seen in the early stages of the disease.

T. Leese

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Author's reply

Sir

I am grateful to Mr Leese for pointing out the error in volume of FFP per standard unit, three of which our patients received daily.

The entry numbers into the Leicester trial are impressive, but is the use of FFP justified in mild pancreatitis which is a self-limiting disease? I understand that the severity prediction criteria used in Leicester include patient age, whereas we prefer those of Osborne, Imrie, Carter (*Br J Surg* 1981; **68**: 758–61), which allow for the predominance of elderly biliary pancreatitis seen in Britain. This may account for the higher incidence of severe pancreatitis in Leicester than in Sheffield (19·4 per cent compared with 11·9 per cent) and consequently our higher mortality.

I accept our numbers are small, but our antiprotease results are undiluted by mild cases receiving FFP and may give the true picture in severe pancreatitis, although larger numbers are needed to be conclusive.

A. J. Goodman

Royal Hallamshire Hospital
Sheffield S10 2JF
UK

Unusual isolated iliac artery aneurysm

Sir

The recent case report by Gilfillan *et al.* (*Br J Surg* 1986; **73**: 375–6) emphasizes that these aneurysms are rare, their presentation unusual and if they rupture the characteristic signs of blood loss may not be present as a result of containment by the gluteal muscles. Recently, a 66-year-old man with a ruptured right iliac artery aneurysm was admitted under our care. The management of this patient emphasized that a ruptured iliac aneurysm can be confused with a ruptured aortic aneurysm and that these lesions may be associated with dilatation of the aorta and iliac arteries making reconstruction technically difficult. It is suggested that if such an aneurysm is suspected an angiogram is performed before exploration to delineate the site of rupture and the appropriate reconstructive procedure.

G. C. Pansini
I. Donini

Which leg for skin grafts?

Sir

I read with interest the article by D. Flook *et al.* regarding which limb skin grafts should be taken from in the surgery for malignant melanoma (*Br J Surg* 1986; **73**: 793–795). I would like to comment that, irrespective of tumour consideration, most surgeons would prefer to harvest the skin graft from the contralateral limb for a different reason. If the skin graft is harvested from the ipsilateral limb then the necessary skin graft dressing is often noted to exert a tourniquet effect which may result in troublesome bleeding at the excisional site which is contributory to haematoma formation under applied split skin grafts. For the same reason, in the surgery of limb trauma where split skin grafting is required, the contralateral limb, though less convenient, is the preferred site.

N. Waterhouse

West Middlesex University Hospital
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UK

Authors' reply

Sir

We are grateful for the interest shown by Mr Waterhouse in our paper and accept that there are many variations available on any surgical technique. We understand his concern with his experience of a tourniquet effect, but we would not be willing to accept proximal venous compression on either leg. A simple OpSite dressing for donor areas has been in widespread use for a number of years, and gives excellent results without circumferential pressure. We do not find haematoma formation under the graft a major problem, since a number of techniques may be used to control troublesome oozing, including uniform pressure to the skin graft with a tailor-made Silastic foam dressing[1] or delayed open grafting[2].

L. E. Hughes
D. Flook

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UK

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Book reviews

Textbook of Surgery 1.

D. C. Sabiston Jr. 270 × 205 mm Pp. 2496. 1986. Philadelphia: W. B. Saunders. £65.00.

Some may dispute whether there is any place for the megalithic, all encompassing textbook of surgery given the insidious contraction of the profession of general surgery and the profusion of excellent and comprehensive texts dealing with the different branches. Many general textbooks escape this by directing themselves primarily at medical students and those sitting higher examinations. This tends to leave them a little short on those nuances and nooks for which any practising surgeon may need to take down a textbook. The question remains, however: can a single textbook be truly and effectively comprehensive? This new edition of Sabiston's textbook comes as close to the ideal as anyone could expect given the difficulties of coordinating 200 very senior authors and producing a book large enough to be comprehensive (2500 pages) yet compact enough to fit into one volume (though it is available as two).

The balance and layout of the book are good and consistent. Orthopaedics, gynaecology and neurosurgery find their own modest places though cardiothoracic surgery occupies an immodestly expansive 530 pages.

Current interests are widely and effectively covered in the many new and the wholly revised old sections. Prostaglandin physiology, hormone receptors in melanoma, conservative management of breast cancer, fibreoptic bronchoscopy, cyclosporin and parathyroid carcinoma were among the topics I chose to look up and I found each authoritatively and readably covered.

The book is well indexed and well referenced. A useful feature of the references is that important entries in the bibliographies have a five line abstract appended, thus helping the reader to avoid futile literature searches. Overall this new edition of Sabiston confidently allows it to retain its pre-eminence whilst at the same time remaining sensibly priced.

A. E. Young

Year Book of Vascular Surgery 1986

J. Bergan and James Yao. 235 × 155 mm. Pp. 379. Illustrated. 1986. Chicago: Year Book Medical Publishers Inc. Distributed by Wolfe Medical Publications Ltd, London. £38.00.

This is a new edition to the Year Book series, confined to surgical aspects of peripheral vascular disease which is now excluded from the Year Book of Surgery. The authors have reviewed all relevant major publications for the years 1984 and 1985, and produced a summary of many of these. Sadly they have included relatively few from outside the USA.

The largest section of the book concerns occlusive lesions of arteries, and would benefit from some further sub-grouping. Other chapters include aneurysms, venous disease and portal hypertension. There is a small but interesting section on new developments, and short chapters on ascites, sympathetics and vascular access for dialysis.

I found this a useful book providing an easy method of ensuring a comprehensive review of the literature. It should find a place on the bookshelf of many vascular surgeons.

M. Horrocks

Surgery of Occlusive Cerebrovascular Disease

R. S. A. Lord. 270 × 185 mm. Pp. 543 + ix. Illustrated. 1986. Oxford: Blackwell Scientific Publications. £72.50.

The author has produced a very thorough discussion on the whole of this subject. This book will be a valuable addition to those libraries where surgery for stroke is carried out. It could be too specialist for the average postgraduate library but will be a great asset for young surgeons taking an interest in this subject. Each chapter is accompanied by a long and useful list of references, although the system of referencing is rather confusing. There are chapters on historical aspects, anatomy and risk factors and reviews of current investigation methods, techniques and results. The overall impression is that this is a thorough review of a specialist subject, rather over-long in parts but valuable to surgeons with a particular interest in cerebrovascular disease.

R. Greenhalgh

Operative Urology. 2nd Edition

John Blandy. 280 × 225 mm. Pp. 259 + viii. Illustrated. 1986. Oxford: Blackwell Scientific Publications. £39.50.

John Blandy is a most prolific author of urological texts in this country and the second edition of his textbook of operative urology, 8 years after the first, will be welcomed by all urological trainees and not a few of their chiefs. His literary style is crisp and forthright and, like all his contributions, eminently readable. In addition, the illustrations (all done by himself) are clear and appropriate and, as far as any textbook can, give a clear idea of the steps of the procedure described.

The indications for the operation are dealt with briefly with mention of special precautions and hazards. The main text concerns the steps of each operation and it is full of practical advice based on his very considerable experience of immense value to the trainee.

In any rapidly developing field, textbooks tend to lag behind the growing edges of the specialty and this is most noticeable in the field of stone surgery where new methods of treatment appear at almost monthly intervals. However, it is important to remember that this book will be read in many countries without access to the most up-to-date equipment including many areas of the UK! Proven methods of surgical management should be learnt by everyone.

In the preface, the author says that 'in the kitchen of surgery the cookbook is a pale echo of assisting and being assisted by the chef'. This cookbook is clearly in the Cordon Bleu class.

J. C. Smith

Anatomy. 1800 Multiple Choice Questions

M. J. T. Fitzgerald, James P. Golden and Maeve Fitzgerald. 210 × 135 mm. Pp. 210. Illustrated. 1986. London: Butterworths. £6.95.

Revised, updated and enlarged from *1600 Questions*, by the same authors, this test-yourself text is ideal for pre-clinical and primary FRCS students. A variety of questions include well labelled illustrations of classical diagrams and separate sections on gross anatomy, histology and neuroanatomy. The embryology section is thin on organ development so embryonic surgeons beware! At 'three for a penny', however, it certainly is value for money and any student knowing all the answers would have a good general anatomical background for clinical studies.

P. H. Abrahams

Tutorials in Surgery 2. 2nd edition

F. G. Smiddy. 215 × 140 mm. Pp. 319 + xii. Illustrated. 1986. Edinburgh: Churchill Livingstone. £14.95.

The first Edition of this book was produced in 1979, and it consists of a series of tutorials grouped into four areas: General Principles, General Surgery, Urology and Arterial and Venous Surgery. Within each of these headings there are sections devoted to individual subjects which are totally independent from one another. Each of the topics could be the subject for oral or written examinations, making this book ideally suited for Fellowship candidates. The majority of the text is an exact duplication of the material printed in 1979 but, despite the gap of 7 years, the knowledge is very valuable. The paper, print and layout show an improvement and each section is easy to read. In a book of this sort I think it is acceptable that there is no index or list of references.

In the General Principles section, carcinogenic agents have been dropped as a topic, and intravenous nutrition has been added. It might have been of more value if the latter topic could have included entero- and peripheral line nutrition. In the General Surgery section pathogenesis of duodenal ulcer has been removed and about half of the topics have been improved. I was surprised to find that there is no reference to primary resection for obstructed carcinoma of the colon.

In Urology the chapters are the same with minimal up-dating although lithotripsy is included. In the last section on Arterial and Venous Surgery there are minor changes improving and up-dating the tutorials. It might have been reasonable to include microvascular surgery to up-date this aspect of the subject.

I would repeat that this is a very valuable book for examination candidates and, at £14.95, it is not expensive.

A. A. Gunn

Basic Surgical Skills. An Introduction to Surgical Procedures

Peter H. Weil. 125 × 175 mm. Pp. 142. Illustrated. 1986. Oxford: Blackwell Scientific Publications. £13.50.

Medical students and house officers are often confused by theatre practice, operative details and common practical procedures. *Basic Surgical Skills* goes some way to filling this gap but, by being too detailed in some areas and incomplete in others, leaves an impression of imbalance.

The first four chapters are simple but informative. However several illustrations here and elsewhere in the text lack legends of sufficient detail to be valuable. The photographs are of poor quality and are not explained at all. The description of digital nerve block is singularly unhelpful.

Pericardial, cul-de-sac or urinary bladder aspiration must be seldom required by such junior staff. Is there any place for the use of an Esmarch tourniquet to manage haemorrhage?

A major criticism of this book is the selection of operations. The 'minor procedures' are acceptable but few would agree that herniorrhaphy is major (especially as fistulectomy and tracheostomy are minor), or that gastrostomy or open heart massage are important major operations for the audience concerned.

Alternative texts such as *The Oxford Handbook* or *Pye's Surgical Handicraft* would be a 'better buy' for the junior doctor or medical student.

J. A. R. Smith

Stoma Care Nursing

Catherine Elcoat. 195 × 125 mm. Pp. 302. 1986. Eastbourne: Holt-Saunders Ltd. £7.95.

This is an excellent book that has the great merit of being written in plain English, totally free of the pseudoscientific and sociological jargon that makes so much modern nursing writing unreadable.

The authoress (as she unashamedly refers to herself in the preface) is a senior stoma care nurse at North Tees General Hospital where she not only practises her speciality but also teaches on the course in stoma care held at that hospital.

The book, which has been well produced and printed by the publishers, consists of 17 chapters covering everything from the history of stoma care through the technical aspects to the psychological and social consequences of stoma surgery. It tells us what a stoma care nurse is, what she does and how she does it. It also reveals just how extensive is the knowledge required by these specialist nurses as evidenced by comments on the influence of a Moslem's position at prayer upon stoma site and the effect of a strict Sikh's eating habits upon stoma function.

Although the preface indicates that this book has been written primarily for Mrs Elcoat's nursing colleagues it is undoubtedly suitable for medical students and practitioners. I think it is one of the best books that I have ever read on stoma care and it deserves to be on the bookshelf of every general surgical ward in the country.

M. H. Irving

A Colour Atlas of Gastrointestinal Endoscopy

K. F. R. Schiller, R. Cockel and R. H. Hunt. 280 × 220 mm. Pp. 240. Illustrated. Hampshire: Associated Book Publishers UK Ltd. £65.00.

This new book by British authors is most welcome. It is an excellent colour atlas of endoscopic photographs, supplemented by a brief descriptive text and occasional line drawings and X-rays. It does not purport to be, and does not replace, the standard texts on endoscopic technique. Diagnostic and therapeutic procedures involving the upper and lower gastrointestinal tract, the bile ducts (including peroperative choledochoscopy) and pancreas are covered. I was particularly impressed by the illustrations and techniques demonstrated for removal of foreign bodies. In a future edition I would hope to see a few illustrations of peroperative endoscopic examination of the intestines and no doubt there will be more illustrations concerning the use of lasers. References are not given in the text but there is a bibliography at the back of the book which might be expanded. This book will inevitably be compared with Blackstone's book on endoscopic interpretation. It is a little less comprehensive than Blackstone but the illustrations are as good and it cost less. A copy of this book should be available in every gastrointestinal endoscopy suite.

D. E. F. Tweedle

Hamilton Bailey's Emergency Surgery. Eleventh Edition

H. A. F. Dudley. 280 × 215 mm. Pp. 726 + xiv. Illustrated. 1986. Bristol: John Wright and Sons Ltd. £60.00.

Although 28 distinguished experts contribute to the eleventh edition of Hamilton Bailey's Emergency Surgery, there is a pleasing uniformity and clarity of text that bears the hallmark of excellent editing. The photographs, radiographs, and line drawings are of excellent quality and illustrate the text well. Whether reading a section or dipping into the book at random the reader is presented with an interesting, clear and logical approach to a particular problem and its management – although several procedures might be considered the domain of the specialist (e.g. emergency neurosurgical and neonatal procedures), it is important to appreciate that referral to such centres cannot always be achieved on a global basis: this book allows the man on the spot to cope with confidence when evacuation to such units is not possible.

At £60 this book is very good value and I submit there is much in it for the established surgeon (I think the first section in particular should be read by all and is an excellent 'refresher course'). I found the chapters on the eye, the ear and emergencies in the tropics and subtropics, which under other circumstances I might have skipped over, interesting and well presented. For surgeons in training, access to this book is a must and every theatre suite should have a copy.

A. L. G. Peel

Essentials of Thoracic Surgery

R. Hurt and M. Bates. 235 × 165 mm. Pp. 270 + xii. Illustrated. 1986. London: Butterworths. £24.50.

This is a compact book of 270 pages with a stiff attractive cover. There are twenty-two chapters. Twenty of these chapters cover aspects There are twenty-two chapters. Twenty of these chapters cover aspects of thoracic surgery including diseases of the lung, chest wall, diaphragm and mediastinum, and an excellent chapter on chest injuries. There is a chapter on cardiac surgery by an invited author. Whilst one can appreciate the desire to include cardiac surgery, it is perhaps unfortunate that the chapter is restricted to discussing ischaemic heart disease and makes no mention of congenital or valvular problems. The last chapter deals with cardiac arrest and seems somewhat out of place in such a specialized book.

Twenty-one of the chapters are contributed by the two main authors, resulting in a highly personal approach. Whilst this could be criticized by surgeons with other views there is little space in such a compact book to present alternative views when dealing with the basics of the speciality.

This book is extremely readable, and the illustrations in general are good and helpful. It is always difficult to reproduce chest radiographs, but the publishers succeed in this book, although it is somewhat irksome that many chest radiographs have been needlessly mounted sideways.

Carcinoma of the bronchus merits greater coverage, particularly the concept of pre-operative staging and the role of mediastinoscopy.

The book represents good value and provides a brief introduction to the speciality for surgeons approaching the fellowship or those preparing to take up a thoracic surgery post. It would not be considered sufficiently comprehensive for those pursuing the speciality.

P. Goldstraw

The Man Behind the Syndrome

P. Beighton and G. Beighton. 275 × 195 mm. Pp. 240. Illustrated. 1986. London: Springer Verlag. £19.90.

Although many would have us eschew clinical eponyms they survive and multiply, having not only a value as shorthand but also as historical curiosities. The authors of this compendium give us 100 syndromes briefly outlined together with a short biography and picture of the architect of each. There are also a further 110 brief unillustrated biographies. Unfortunately the syndromes chosen are primarily of relevance to paediatricians, being congenital vagaries rather than surgical diseases.

The book is prefaced by the quotation: 'There is no history, only biography' which the authors attribute to 'Thomas Carlisle' (presumably they mean Carlyle) when in fact the aphorism is Emerson's, which makes one worry about the accuracy of other details in the book. The book itself bears out the falsity of the aphorism in this context, for the biographies tell us nothing of the syndromes and vice versa. All but a few of the illustrations are photographs and, like the text, are formal, blank and unrevealing.

A. E. Young

Notices and announcements

Meetings

17–18 January 1987
Meeting of the American Academy of Head, Neck and Facial Pain and Temporomandibular Joint Orthopedics
Washington, DC, USA
Information: American Academy and Board of Head, Face and Neck Pain and TMJ Orthopedics, Medical Towers Building, Suite 803, 255 S 17th Street, Philadelphia, PA 19103, USA

24–25 January 1987
Hong Kong Surgical Forum
Hong Kong
Information: Forum Secretary, c/o Department of Surgery, University of Hong Kong, Queen Mary Hospital, Hong Kong

8–13 February 1987
Sixth Biennial General Scientific Meeting of the Association of Surgeons of South East Asia
Bangkok, Thailand
Information: Dr. P. Gojaseni, FRCS, The Scientific Chairman, Association of Surgeons of South East Asia, c/o The Department of Surgery, Ramathibodi Hospital, Bangkok, Thailand

21–24 March 1987
21st Annual Scientific Meeting of the European Society for Clinical Investigation
Elsinore, Denmark
Information: Congress Office, ESCI-87 c/o D. I. Barry, Department of Psychiatry, 06234 Rigshospitalet, 9 Blegdamsvej, DK-2100 Copenhagen Ø, Denmark

23–25 March 1987
International Meeting on Heart Transplantation, Total Artificial Heart and Assist Devices
Brussels, Belgium
Information: E.C.C.O, Rue Vilain XIV 17a, B-1050 Brussels, Belgium

1–3 April 1987
Association of Surgeons of Great Britain and Ireland
Liverpool, UK
Information: Mr B. T. Jackson, Association of Surgeons of Great Britain and Ireland, Royal College of Surgeons, 35/43 Lincoln's Inn Fields, London WC2A 3PN, UK

28 March–4 April 1987
Fifth Cardiosurgical Symposium
Zürs, Austria
Information: Professor M. Deutsch, II. Chirurg. Univ.-Klinik Wien, Spitalgasse 23, A-1090 Vienna, Austria

5–10 April 1987
American Society of Colon and Rectal Surgeons Annual Convention
Washington, DC, USA
Information: Miss H. Gibson, 615 Griswold, 1717 Detroit, MI 48226, USA

6–8 April 1987
Annual Meeting of the American Association for Thoracic Surgery
Chicago, Illinois, USA
Information: American Association for Thoracic Surgery, 13 Elm Street, Manchester, MA 01944, USA

27–28 April 1987
International Symposium on Reoperative Infrarenal Arterial Surgery
Rigshospitalet, State University Hospital, Copenhagen, Denmark
Information: International Symposium on Reoperative Infrarenal Arterial Surgery, Department of Surgery D, Section of Vascular Surgery, Rigshospitalet, State University Hospital, 9 Blegdamsvej, DK-2100 Copenhagen Ø, Denmark

9–15 May 1987
Digestive Disease Week of the American Gastroenterological Association
Chicago, Illinois, USA
Information: Registration Supervisor, Slack Inc., 8900 Grove Road, Thorofare, NJ 08086, USA

10–13 May 1987
Joint Annual Meeting of the American Lung Association, the American Thoracic Society and the Congress of Lung Association Staff
New Orleans, Louisiana, USA
Information: American Thoracic Society, 1740 Broadway, New York, NY 10019, USA

10–13 May 1987
XXII Congress of the European Society for Surgical Research
Aarhus, Denmark
Information: Aarhus Turistforenings Kongresbureau (Convention Bureau), Radhuset, DK-8000 Aarhus C, Denmark

20–23 May 1987
78th Annual Meeting of the American Association for Cancer Research
Atlanta, Georgia, USA
Information: Margaret Foti, American Association for Cancer Research Inc., Temple University School of Medicine, West Building, Room 301, Broad and Tioga Streets, Philadelphia, PA 19140, USA

25–28 May 1987
European Society for Therapeutic Radiology and Oncology Sixth Annual Meeting
Lisbon, Portugal
Information: Professor Dr E. van der Schueren, Department of Radiotherapy, Kapucijnenvoer 35, 3000 Leuven, Belgium

10–12 June 1987
69th Meeting of the Endocrine Society
Indianapolis, Indiana, USA
Information: The Endocrine Society, Annual Meeting Office, 428 E Preston Street, Baltimore, MD 21202, USA

10–13 June 1987
Third International Conference on Malignant Lymphoma Current Status and Prospects
Lugano, Switzerland
Information: Dr F. Cavalli, Head Division of Oncology, Ospedale San Giovanni, CH-6500 Bellinzona, Switzerland

15–19 June 1987
Advanced Hepato-Pancreatico-Biliary Surgery
Lund, Sweden
Information: Professor S. Bengmark, Box 5121, S-220 05 Lund 5, Sweden

22–26 June 1987
Peritoneum and Peritoneal Access
Lund, Sweden
Information: Professor S. Bengmark, Professor of Surgery, Box 5121, S-220 05 Lund 5, Sweden

24–28 June 1987
Annual Meeting of the Western Thoracic Surgical Association
Colorado Springs, USA
Information: Western Thoracic Surgical Association, 13 Elm Street, Manchester, MA 01944, USA

7–8 July 1987
Blood Flow '87 (Biological Engineering Society – Blood Flow Group)
University of Leeds, UK
Information: Mr R. Price, Department of Medical Physics, Leeds General Infirmary, Leeds LS1 3EX, UK

31 August–4 September 1987
Surgical Efficiency and Economy
Lund, Sweden
Information: Professor S. Bengmark–SEE, Box 5121, S-220 05 Lund 5, Sweden

9–11 September 1987
Clinical Controversies in Inflammatory Bowel Diseases
Bologna, Italy
Information: Organizing Secretariat, SO.GE.PA.CO. Spa. piazza Constituzione, 5/c, 40128, Bologna, Italy

15–18 September 1987
The British Society of Gastroenterology Jubilee Meeting
London, UK
Information: The Administrative Secretary, The British Society of Gastroenterology, 3 St Andrew's Place, Regent's Park, London NW1 4LB, UK

Leading article

Br. J. Surg. 1987, Vol. 74, March,
155–156

Anti- reflux operations: how do they work?

In this issue Bancewicz and his colleagues suggest that lower oesophageal sphincter (LOS) pressure and the length of intra-abdominal oesophagus bear no relationship to reflux control after fundoplication. How then does an antireflux operation control reflux? To try and answer this question, it is necessary to consider briefly current views on the mechanisms leading to gastro-oesophageal reflux disease.

It is well established that there is a physiological and anatomical lower oesophageal sphincter interposed between the positive pressure in the stomach and the negative pressure in the intra-thoracic oesophagus[1]. It is now regarded as established that reflux occurs in everyone, particularly after meals and very infrequently at night. How can we reconcile the presence of a lower oesophageal high pressure zone with such 'physiological' reflux? The answer to this paradox came with the development of technology which allowed prolonged measurement of LOS pressures[2]. Such measurements have shown that the sphincter undergoes periods of sudden and complete relaxation. These transient lower oesophageal sphincter relaxations last for 5–30 s; it is during such relaxations that physiological reflux tends to occur[3]. The mechanisms by which this reflux might then go on to cause gastro-oesophageal reflux disease include the following[4]. (1) Poor oesophageal emptying allows prolonged contact between refluxed material and oesophageal mucosa. This is seen in its most extreme form in adynamic oesophagus associated with scleroderma. However, some patients with primary reflux disease also have delayed oesophageal emptying[5]. (2) Duodenogastric reflux is also a normal event[6]. The role which duodenal contents mixed with gastric juice may play in the development of reflux disease in man is uncertain.

The fact that many patients with reflux disease have no basal tone recordable in their LOS led to the concept that loss of sphincter tone was the primary determinant of reflux disease. However, many patients with reflux disease have normal basal LOS tone, as shown again by Bancewicz and his colleagues.

When transient LOS relaxation occurs in patients with reflux disease, it is more likely to be followed by a reflux event than in normal control patients[2]. The episodes of transient relaxation appear to be mediated by a vagovagal reflex centred in the dorsal nucleus of the vagus. The reflex is initiated by stretch receptors in the gastric fundus, leading to afferent discharge to the dorsal nucleus of the vagus, and subsequent efferent discharge to non-adrenergic, non-cholinergic inhibitory fibres to the lower oesophageal sphincter muscle. This has been dubbed the 'belch reflex'[7]. One reason for the more frequent initiation of this reflex in patients with reflux disease may be the delayed gastric emptying which occurs in a substantial proportion of them[8]. When sphincter pressure does fall to zero, reflux events may also occur more commonly in reflux disease patients because of derangements associated with the sliding hiatus hernia which is present in many of them. Of course, transient increases in abdominal pressure, as in coughing, can also lead to reflux, but this is a much less frequent mechanism in patients with reflux disease.

Thus, reflux occurs mainly when there is no recordable LOS pressure. This loss of tone may be chronic (which in itself may be a result of reflux damage) or transient, with increased numbers of such episodes occurring in reflux patients. The refluxed material may cause oesophageal mucosal damage, leading to further sphincter hypotension, thus setting up a vicious cycle.

What then are the possible mechanisms of action of anti-reflux operations? It must be acknowledged that all antireflux operations have anatomical/mechanical effects on the region of the oesophagogastric junction. For example, nearly all antireflux operations narrow the angle of His and most of them also restore a length of intra-abdominal oesophagus. It is difficult to separate the action of these two mechanisms but the flap valve effect of the acute angle and of the exposure of a length of lower oesophagus to abdominal positive pressure may both play a role in reflux prevention (although the study by Bancewicz *et al.* (*Br J Surg* 1987; 74; 162–4) suggests that the latter mechanism has a relatively minor role). In total fundoplication the 'buried'

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oesophagus acts as a one-way valve; this is effective against large increases in intragastric pressure even when constructed within the negative pressure environment of the thorax, and even when studied *ex vivo*. These anatomical/mechanical effects may be most important in preventing reflux when LOS pressures fall to zero. However, antireflux operations also affect pressures in the LOS region and this may be a more important function.

All antireflux operations in current practice have been reported as increasing sphincter tone in most patients. However, to prevent free reflux it is probable that a sphincter tone of about 5 mmHg is sufficient. If more vigorous abdominal pressure increases occur, then the anatomical/mechanical effects mentioned above probably come into play to counteract reflux. Also, all of these operations probably prevent distension of the gastric fundus to some degree. This is particularly true of total fundoplication but to a lesser extent it applies to partial fundoplication operations and insertion of the Angelchik prosthesis. Therefore the stimulus for transient LOS relaxation may be attentuated or even abolished by antireflux surgery. Furthermore, if sphincter relaxation does occur, the pressure may not fall to zero after fundoplication[9]. Finally, the prevention of distension by the antireflux operations may also directly bolster the lower oesophageal sphincter preventing it being weakened by distraction[9,10].

The explanation for the findings of Bancewicz *et al.* might then be as follows. First all of their patients had sufficient LOS tone postoperatively (5 mmHg) to prevent free reflux. Second, intra-abdominal length may be less important than the flap valve or other mechanical effects of fundoplication. Third, their patients with recurrent reflux may have failed for other reasons, such as poor oesophageal emptying, composition of refluxate, and failure to prevent excessive episodes of transient LOS relaxation.

Does any of this knowledge carry practical implications for surgeons? What should we assess before a patient comes to antireflux surgery? The minimum requirement is proof that the patient has reflux disease. If endoscopy reveals erosive or ulcerative oesophagitis and the patient has heartburn and regurgitation, then outside the context of a clinical study, probably nothing further is required (provided that the surgeon keeps the area of the oesophagogastric junction loose). However, if a patient has atypical symptoms, and in particular chest pain and/or dysphagia, or less than erosive oesophagitis on endoscopy, then further investigation is indicated. Objective evidence for pathological reflux should be sought through pH monitoring and primary oesophageal motility disorders should be excluded by manometry. Most surgeons with an interest in this area have seen patients who have had antireflux surgery performed inappropriately for non-reflux related motility disorders, such as achalasia or diffuse spasm. Also, dysphagia can occur following anti-reflux surgery for scleroderma associated reflux if care is not taken to avoid a tight oesophagogastric junction.

Antireflux operations are successful in a majority of patients. That still means that in a minority of patients antireflux operations fail. The factors or interaction between factors influencing the success of antireflux operations are poorly understood. There is plenty of room for new knowledge in this area.

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Review

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Twenty-four hour ambulatory oesophageal pH monitoring: an update

Gastro-oesophageal reflux (GOR) is a common condition the diagnosis of which is confused by variable symptomatology, equivocal reflux on radiological investigations and often little evidence of macroscopic oesophagitis on endoscopy. During the last 30 years various tests have been devised to investigate the presence and severity of reflux and its relationship to symptoms. These tests include oesophageal manometry[1], the Bernstein acid perfusion test[2], the Tuttle test[3] and reflux provocation tests[4]. All, however, suffer to a degree from a lack of sensitivity or specificity, essential for an accurate diagnosis of this disorder.

In the mid 1950s, with the advent of stable intra-oesophageal pH sensitive glass electrodes[5], long term pH monitoring of the distal oesophagus became possible. This enabled continuous measurement of oesophageal pH with positive identification of gastro-oesophageal reflux[6,7]. In the mid 1970s DeMeester, Skinner and Johnson were among the first to advocate long term 24 h pH monitoring in the distal oesophagus as a sensitive test in the evaluation of gastro-oesophageal reflux[8–10]. Oesophageal pH was measured using a glass pH sensitive electrode introduced through the nose and positioned 5 cm above the manometrically determined lower oesophageal sphincter or high pressure zone. This method of positioning continues to be used almost universally for this investigation. pH was continuously recorded for 24 h on a paper chart. Subjects were allowed to eat and drink normally but were limited to the confines of the recording equipment and the investigatory laboratory.

Symptoms of GOR are sometimes reported only during normal daily activities and may be induced by the variable life styles, diet, behavioural and physical activities of patients suffering from the disorder[11–13]. Investigators were aware of the immobility imposed by hospitalization of patients undergoing 24 h pH monitoring for the detection of GOR, hence there has been a general trend towards producing measuring equipment which enables pH measurement in the patients' home environment.

The first ambulatory system for distal oesophageal pH monitoring was developed in 1980[14] but did not show differences in reflux between hospital and home monitoring. However the method employed to monitor pH was a telemetered signal from a glass electrode which had a range of only 100 m and did not allow truly ambulatory recordings. Two years later using a radiotelemetric technique and portable equipment we found that gastro-oesophageal reflux in patients with oesophagitis was more severe, more frequent and of longer duration during ambulatory studies than during similar tests performed in hospital[15].

Ambulatory pH monitoring is now performed routinely in many centres throughout the world. Tests may be purely diagnostic, in which case patients are encouraged to live as normal a lifestyle as possible during the test. In order to correlate symptoms with reflux and identify parameters that provoke reflux there should be as few restrictions as possible. Patients are usually allowed to eat, drink and smoke freely throughout the study period apart from minor restrictions of acid foods which may lead to overestimation of acid reflux. If, however, tests are being performed to evaluate medical or surgical therapy, although it is desirable to maintain the ambulatory nature of the investigation, it may be advisable to standardize some of the factors that provoke reflux such as food and drink. A more standardized schedule for patients may avoid the pitfalls of poor reproducibility when comparing new drugs or surgical procedures.

In symptomatic patients many controversies still exist about the exact nature of fluids refluxing into the oesophagus. There is some evidence to suggest that in certain patients reflux may be a mixture of acid, pepsin and sometimes bile which may cause severe symptoms. As the pH may be only slightly acid or even neutral these may not be detected as reflux events and can cause errors in the correlation of symptoms and reflux.

Gastro-oesophageal reflux is also known to occur in normal asymptomatic subjects as well as in symptomatic patients and this confuses the positive detection of abnormal or pathological reflux in the investigation of patients with symptoms[9,16,17]. Scoring systems, normality charts and guidelines of upper limits of physiological reflux have been compiled during the development of oesophageal pH monitoring but have in the main been restricted to studies in the laboratory which may not be relevant to ambulatory tests[18–20]. Only more recently have investigations been performed on normal subjects under ambulatory conditions[15,21], the importance of which has been highlighted in a recent report[22]. It is these studies that may provide normal control data for comparison with ambulatory measurements on patients. Attention has also been paid to the incidence of GOR related to increasing age[23] but no significant differences have as yet been demonstrated. Controversy still exists as to the 'correct' limits of normality and universally accepted guidelines are still needed about the upper limit of GOR that is acceptable in normal individuals.

The popularity of ambulatory pH monitoring has increased dramatically during the past 5 years and this has gone hand in hand with the development of new equipment to facilitate the collection of data. It is estimated that there are now approximately 12 major manufacturers of ambulatory pH monitoring equipment in Great Britain, North America and Europe. There must also be at least as many if not more systems that have been developed by hospitals and research institutions[24]. It seems appropriate therefore to evaluate current practices associated with ambulatory pH monitoring as well as available measuring systems. Of importance also is patient acceptability and the state of the investigation in relation to patient management.

Evaluation of equipment and techniques

Electrodes

Since the introduction of the Beckman glass electrode (Beckman RIIC, High Wycombe, Buckinghamshire) in 1969 this electrode has seen widespread use for *in vivo* pH tests. However, owing to the size and nature of the electrode and the fact that an agar/calomel reference electrode is necessary to ensure stability, it is doubtful whether this electrode will see much use in ambulatory investigations. Recently, new glass electrodes have been developed (Russell pH, UK and Ingold, Switzerland) which allow the use of silver–silver chloride skin electrodes for reference and which have been designed to provide more comfort to the patient during the test. This has been achieved by

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Table 1 *Electrode specification for oesophageal pH monitoring*

	Probes				Radiopill	
	Glass	Antimony	Combined/ glass	Plastic		
Dimensions (mm)	1·6–5	1·8–4	3–4·5	1–2	Dimensions (mm)	28 × 7·8
pH range	0–12	1–10	0–12	4–9	Frequency (kHz)	430 ± 30
Sensitivity (mV)	0–30	0–500		−200 to +100	Sensitivity (kHz/pH unit)	2–4
Response time (98 per cent) (s)	Typically 10–45	<30	<25	<2	pH range	1–9
Impedance (MΩ)	1·5–500	<1	500	1–10	Response time (s)	<4
Reference electrolyte	None	None	KCl/ Friscolyte	None	Reference electrolyte	NaCl/KCl
					Battery life (days)	40
Repair facility	None	Disposable		Available for research only at present	Repair facility	Repairs effected by supplier
Price range	£80–300	£30–80	£200–300	£25–75	Price range	£150–250

reducing the electrode diameter and by using more flexible cables. Further miniaturization has produced the 1·8 mm diameter MI506 glass electrode (Micro Electrodes Inc.). This is particularly useful for paediatric measurements although its response time is slow and its cost relatively high. *Table 1* is a summary of the range of electrodes in common usage at the present time. An estimate of current prices is also given but these should be used for guidance only and may change with market trends.

Combined electrodes for intra-oesophageal pH measurement which overcome the need for external references have obvious advantages over those without. The technical difficulties of producing combined electrodes of sufficiently small diameter which are both reliable and comfortable to the patient have lead to relatively poor development in this area. Two combined pH sensors are currently available from commercial outlets; both are glass electrodes with an integral KCl reference electrode housed near the tip of the probe (Ingold 440M4 and 440M3 and GK2801C, Radiometer, Denmark). These electrodes offer continuous recording with only one cable connection to the recording device and are reported to perform satisfactorily[25,26].

Monocrystalline antimony electrodes (Synectics Ltd, Sweden) have the advantage of smaller size and greater patient comfort. The introduction of monocrystalline electrodes instead of the earlier polycrystalline types has improved stability and reliability. The disadvantage of this type of electrode is a relatively short life of approximately 100 h as the pH sensing process is corrosive, this both oxidizes and removes metallic antimony from the surface of the electrode[27]. A further disadvantage of antimony electrodes is the greater possibility of contamination of the pH sensitive surface with food debris and internal secretions due to the small physical size of the electrode surface. Antimony electrodes are also incompatible with equipment designed for glass electrodes because of a ten-fold difference in output voltage and a low impedance; thus some modification may be necessary to equipment not designed for this type of electrode.

The recently developed pH sensitive radiotelemetry capsule (Remote Control Systems, London, UK) is a stable reliable glass pH sensor with an integral reference cap. The capsules have long duration (40 days with one battery) and may be refitted with battery, reference caps and internal fluids to give an almost indefinite life[28]. The advantages of this device over conventional electrodes are that it is ingested by normal deglutition and has a large pH sensitive glass area giving more rapid response time and resistance to contamination. The capsule also has an internal reference electrode thus offering cable free measurement. One disadvantage of the radiocapsule is that in order to measure oesophageal pH a tether is necessary to prevent propulsion of the capsule into the stomach and this can cause problems during eating by the presence of the tether in the mouth. Signal loss or interference from other radio sources may also be a potential problem but this has been largely overcome by the introduction of sophisticated electronic receiving equipment.

Improvements in construction of pH radiocapsules have led to improved reliability and stability and the use of these devices is now becoming more common[23,29,30]. pH radiocapsules may also be used in gastric studies[31] and untethered in other parts of the gastrointestinal tract[32–4], a use as yet not extensively explored.

Recorders

With the advent of modern microchip technology, ambulatory recorders have seen much development in recent years. Recorders are of two basic types: solid state or tape. The choice of recorder depends on user requirements; the weight, physical size and mode worn by patient are important as this affects the degree of ambulation that is possible. In general, equipment needs to be of a size that can be carried without discomfort or awareness, such as for example a personal stereo tape player. The weight of recorders should be less than 1 kg or patient comfort and mobility may be hampered, heavy equipment supported by shoulder straps may not allow for truly ambulatory monitoring. *Table 2* is a summary of recorders currently available in Great Britain. There are also other systems available in Europe and North America most of which have similar facilities to the British systems.

Event marking facilities enable patients to indicate symptoms, these may be a simple push button or alternatively a key panel to discriminate various different symptoms associated with GOR. Some recorders also attempt to identify upright and supine positions automatically. The use of complex event systems may be confusing to patients and may draw attention to symptoms thereby overestimating their severity. Automated posture assessment also has problems with the accurate determination of true posture and may therefore be misleading.

In many cases the use of a simple patient diary will suffice to indicate important events during the test. The effect of meals, physical activity as well as wake and sleep periods can all be easily recorded by most patients using this method thus avoiding the complication of a confusing keyboard on the recorder.

Three recorders available have a multi-channel capacity. The first is the Proxima 2 (M and M, Bologna, Italy) which has dual pH measurement facilities, the second the Incomed tape recorder (Vilvoorde, Belgium) which allows for dual pH and triple pressure measurement, although the complex oesophageal probe is of a relatively large diameter which may be uncomfortable and perhaps not entirely suitable for ambulatory recordings. The third machine is the Novo Memolog (Novo

Table 2 *Recorder specification for oesophageal pH monitoring*

	Novo	Ormed	Oxford	Synectics	Warwick instruments
Dimensions (mm)	150 × 156 × 42	145 × 90 × 40	155 × 90 × 45	155 × 90 × 33	150 × 90 × 45
Weight	1·05 kg	320 g	600 g	300 g	400 g
Type of recording	Digital	Digital	Digital	Digital	Analogue – needs additional recorder (eg. Oxford Medilog or Reynolds Pathfinder)
Battery life (h)	100	>40 or rechargeable	40		40
Recording duration	0·5 h–68 days	27 h	24 h	24 h	24 h
Sampling rate	Variable 0·20 s–8 min	8 s	6 s	4 s or adjustable	Continuous
Memory size (kbytes)	12	12	16	24	Not applicable
Electrodes	Glass–various	Various–glass	Glass pH radiopill or Glass pH electrodes	Monocrystalline Antimony or glass	Radiopills 250–500 kHz tunable
No. of recording channels	2	1	1	1 or 2	1
Symptoms marker	Push button	Push button	Push button	Push button	No
Display	Liquid crystal -pH	None	Liquid crystal pH, time, signal strength event marker	liquid crystal -pH	None (additional plug-in monitor unit supplied)

Industries, Copenhagen) which has two interchangeable channels to facilitate dual recordings of pH, temperature, pressure and with a special transducer even gamma emissions can be recorded.

Radiotelemetry receivers and recorders were initially limited to private development[35,36] although these systems are now available from commercial outlets. (Warwick Instruments, Nottingham, UK; Gaeltec, UK). Recently a receiver/recorder has been developed specifically for use with the new pH sensitive radiotelemetry capsule (Oxford Medical Systems). This unit houses in a single case a combined receiver recorder facilitating 24 h recording of oesophageal pH. This equipment also has a glass electrode input as an alternative facility for use in patients where radiocapsules may not be appropriate.

Replay and analysis

Replay from the ambulatory recorder is usually through a dedicated replay unit designed specifically for its own recorder. Replay can be a simple pen driver chart display (Ormed Ltd) or a complex microprocessor driven visual display unit and digital printer (Sandhill, Delmar, Synectics).

Analysis of the recording depends entirely on criteria stored within the calculating facilities of replay systems and there has been considerable debate as to the most appropriate analysis to discriminate pathological from physiological reflux.

Although many users still utilize the DeMeester scoring system[9], there is considerable debate about whether this is entirely suitable for ambulatory records as it was devised from only 15 normal subjects undergoing 24 h monitoring in a laboratory. The scoring calculations are also heavily weighted towards supine reflux as the most important discriminatory factor of pathological reflux.

Most analysis systems give reflux calculations of frequency, duration, percentage time below pH 5 and pH 4 or other selected discriminant. Reflux indices can also be calculated, the Frequency Duration Index (FDI)[37] is available in the Oxford replay system. Cumulative frequency plots have been also devised[29] which may be useful in the discrimination between physiological and pathological reflux. Automated analysis does ensure repeatable reliable assessment of data as well as saving considerable time in the manual analysis of 24 h recordings.

Patient acceptance

The final and possibly most important consideration in ambulatory pH monitoring is patient acceptability. If patients are not entirely happy with probes or tethers or the obtrusive nature of the measurement they may not be truly ambulant. The most important factors are cosmetic acceptibility and physical comfort. Nasogastric probes are difficult to conceal effectively and patients may be sufficiently embarassed to keep them at home. Radio pills or probes may also be uncomfortable when positioned nasally or orally, thus preventing normal eating. This may cause problems in the expression of typical reflux patterns especially in cases where post-prandial reflux is an important factor.

Clinical and diagnostic uses

Twenty-four hour ambulatory pH monitoring is widely advocated for the diagnosis of gastro-oesophageal reflux. Acid reflux can be demonstrated in patients with a negative barium swallow or a normal endoscopy. Twenty-four hour monitoring can identify types of reflux such as upright, supine or combined[10,38] and is also useful in the correlation of symptoms with reflux. This is important in the differential diagnosis of the disease in comparison with other upper gastrointestinal conditions[39,40] or chest pain thought to be cardiac in origin[41,42].

Twenty-four hour monitoring is also useful in the management of patients. It can identify certain factors which may be important such as food, exercise or posture in the stimulation or potentiation of reflux events. For example some patients have been found to reflux only during gardening or other similar exercises after meals and simple dietary advice can often control symptoms. Long term pH monitoring is also useful in the assessment of medical and surgical therapy. Studies have been performed on objective improvement of reflux on antacid and H_2 receptor therapy[43–6]. The reduction of reflux after surgery has also been investigated[47,48] and new techniques such as the Angelchik anti-reflux prosthesis have been evaluated by assessment of reflux both pre- and postoperatively[49,50].

Thus, ambulatory pH monitoring is a useful diagnostic tool in the evaluation of symptoms, treatment and new drugs in the management of gastro-oesophageal reflux. However, there are as yet still no universally accepted standards for the definition of pathological reflux such as the normal ranges found in other clinical investigations. There is still some debate as to whether a 24 h period is essential to the positive diagnosis of reflux and there have been moves towards a shorter test, some centres advocating 15 or 8 h tests as being acceptable for diagnosis[51,52].

Ambulatory pH monitoring of the distal oesophagus is now held to be the gold standard for the investigation of gastro-oesophageal reflux. The increase in diagnostic yield of this investigation has been demonstrated by many centres. The advantages over other tests has been founded on good scientific evidence and should ensure that pH monitoring has taken its place as a standard investigation together with other tests of oesophageal function.

The advent of portable equipment has made measurement considerably easier and is here to stay whatever the final format of the test becomes. The introduction of new technology into the manufacture of pH sensitive electrodes and radiopills is still advancing rapidly and will enhance the comfort and acceptability of the test by smaller and less bulky transducers. pH monitoring is also less expensive than either endoscopy or radiology and is relatively easy to perform, not necessarily requiring the services of a doctor to administer the investigation. Analysis can be automatic and microprocessor controlled units are becoming relatively inexpensive, another time and labour saving process.

Ambulatory pH monitoring is now available in referral centres and major hospitals together with endoscopy and radiology as standard investigations for symptoms of GOR. In future, with less expensive and easy to operate equipment becoming available it may become feasible to incorporate this test into the standard battery of investigations offered to the district hospital physician or surgeon as part of the general diagnostic gastroenterological service.

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The lower oesophageal sphincter after floppy Nissen fundoplication

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The pressure and intra-abdominal length of the lower oesophageal sphincter (LOS) were measured by oesophageal manometry before and after floppy Nissen fundoplication (FNP) for intractable gastro-oesophageal reflux. Control of reflux was assessed by 24 h pH recording and endoscopy. It was complete in 67 cases (84·8 per cent) in this non-consecutive series. In the group as a whole LOS pressure increased significantly after FNP, but the intra-abdominal length did not. LOS pressure decreased in 21 cases of whom 16 (76·2 per cent) still had perfect reflux control. Likewise, intra-abdominal length decreased in 41 cases of whom 36 (87·8 per cent) had good reflux control. There was no evidence of a compensatory increase in length to account for reflux control when LOS pressure decreased. When a length–pressure diagram was plotted for the postoperative measurements no clear separation of those with persistent reflux could be seen. These results suggest that the measured changes in LOS pressure and length following FNP are an artefact of surgery rather than the means by which the operation controls gastro-oesophageal reflux.

Keywords: Lower oesophageal sphincter, gastro-oesophageal reflux, Nissen fundoplication

Although the mechanisms which prevent gastro-oesophageal reflux are now better understood than formerly the function and nature of the lower oesophageal sphincter (LOS) still cause controversy. At present the pressure of the LOS and the length exposed to the pressure environment of the abdomen are thought to be the most important factors which prevent gastro-oesophageal reflux[1–3]. These two factors are also thought to be important in determining the principles of anti-reflux surgery[1,2,4]. Thus there is a tendency to assess the effectiveness of different or new operations by their ability to increase the pressure and length of the LOS. The assumption is therefore made that operations which produce better mechanical effects defined in this way are likely to produce better clinical results.

In assessing the results of the Nissen fundoplication during recent years we have been impressed by the variability of the measured mechanical effects. In addition control of reflux has borne an inconstant relationship to the length and pressure of the LOS. The purpose of the present communication is to report these inconsistencies and to comment on their implications.

Patients and methods

Seventy-nine patients (forty men; thirty-nine women) with a median age of 50 years (range 21–71) were studied before and 2·8–45·5 months (median 7·8 months) after floppy Nissen fundoplication for intractable gastro-oesophageal reflux. All patients had the diagnosis of gastro-oesophageal reflux confirmed by endoscopy and 24 h pH recording. Energetic treatment with a variety of medications, including combinations of high doses of H_2 antagonists, alginate/antacid preparations, bethanechol and metoclopramide, was given for a minimum of 6 months before surgery was suggested. At operation a loose 360° fundoplication was done around a 50 FG mercury bougie as described by Donahue and Bombeck[5]. Care was also taken to produce a short (2–3 cm) wrap.

All patients underwent oesophageal manometry before and after operation at the same session as pH recording. The manometry was performed using standard low compliance equipment. A commercially available multilumen catheter (Arndorfer Medical Specialities, Greendale, Wisconsin, USA) was used throughout. This had a central large channel (1·6 mm diameter) and 8 smaller channels (0·8 mm diameter) for pressure measurement. The catheter was perfused with water from an Arndorfer pneumohydraulic pump at a rate of 0·6 ml/min. Pressure recordings were made from three radially spaced lumens 5 cm from the catheter tip and from two additional side holes at 5 cm intervals.

The LOS pressure was measured by a station pull-through method. This has been previously found to be superior to the rapid pull-through method and its accuracy and reproducibility has been reported from this laboratory[6]. The mean barrier pressure (MBP), the difference between gastric and oesophageal pressure, was calculated from the mean of ten, preferably consecutive, end expiratory pressures at the level where maximum end-expiratory pressure was recorded. Separate measurement was made from each of the three recording channels and the MBP was taken as the mean of the 30 values thus obtained. Results were expressed in mmHg. The length of the LOS was also recorded as well as its relationship to the pressure inversion point to determine its intra-abdominal component.

For the purpose of this study reflux control was defined as complete resolution of all symptoms, normal gross endoscopic appearances and normal values for 24 h pH recording at the time of postoperative assessment.

Results were analysed by non-parametric statistical methods. The median value and the range has been expressed for each variable. The Wilcoxon matched-pairs signed-ranks test was used to assess potentially significant differences.

All subjects gave fully informed consent and the investigation methods were approved by the Ethical Committee of the Salford Health Authority.

Results

The mean barrier pressure was significantly increased ($P < 0{\cdot}001$) after operation for the group as a whole (*Figure 1*). The median value before operation was 7·5 mmHg and 12·7 mmHg afterwards. In contrast the length of the LOS below the pressure inversion point (the 'intra-abdominal' length) was slightly decreased although this small change was not statistically significant (*Figure 2*). Sixty-seven patients (84·8 per cent) met the criteria for reflux control and 12 (15·2 per cent) did not.

In 21 cases the MBP was decreased or did not change after operation. These results are shown graphically in *Figure 3*. Despite this lack of measured improvement, reflux was controlled in 16 cases (76·2 per cent). There was no evidence of

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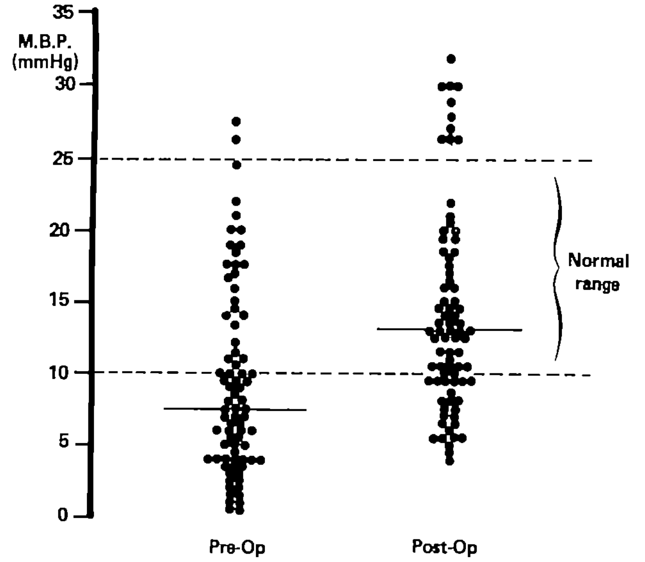

Figure 1 *Mean barrier pressure in 79 patients before and after Nissen fundoplication.* P < 0·001 (*Wilcoxon*)

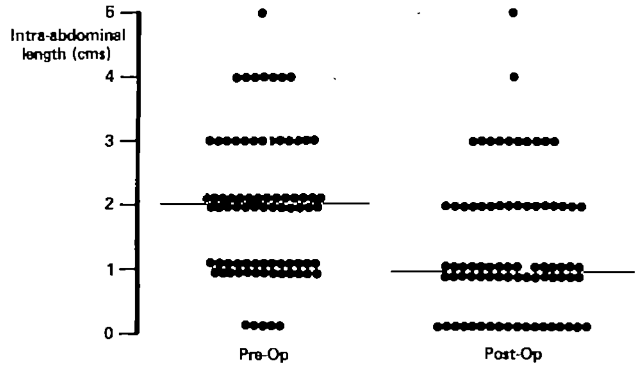

Figure 2 *Length of the LOS below the pressure inversion point – the 'intra-abdominal' length in 79 patients before and after Nissen fundoplication, n.s.*

an increase in the intra-abdominal length in these cases which might have compensated for the lack of change in the MBP. Indeed reflux was controlled in 14 of the 18 (77·8 per cent) cases in whom neither pressure nor length increased. Overall the intra-abdominal length was decreased in 41 cases of whom 36 (87·8 per cent) had complete reflux control.

In *Figure 4* we have plotted the relationship between MBP and intra-abdominal length and have indicated those who had reflux control and those who did not. The curve on the graph is taken from DeMeester's data[7] and indicates the combination of pressure and length required to control reflux. Those below the line would be expected to have reflux. This sort of comparison of data between centres is subject to quantitative error since methods of measurement, particularly of LOS pressure, inevitably vary somewhat from one laboratory to another despite attempts at standardization. However, this does not affect the general principles of reflux control and one would expect to see similar trends from different laboratories if length and pressure are the major factors governing reflux control. Quite obviously our own postoperative data do not confirm the principles outlined by DeMeester since it is impossible to construct a curve which defines a boundary between those with reflux and those without.

Discussion

The mechanisms which prevent gastro-oesophageal reflux in healthy people have recently been reviewed by Skinner[8]. He has emphasized the importance of many factors including the lower oesophageal high pressure zone and the intra-abdominal length of the oesophagus. The relative importance of these factors is of great practical importance to the surgeon who is concerned with improving the current track record of anti-reflux surgery. Without a clear understanding of what to measure and how to interpret the measurements it is unlikely that successful new operations will be devised.

In recent years there has been a tendency to report the results of reflux repairs in terms of clinical results and the effect of the procedure in increasing the pressure of the lower oesophageal sphincter. The implication is that a low pressure is necessarily a bad thing and a higher pressure must therefore be good. Many studies have not even looked at the length of the sphincter

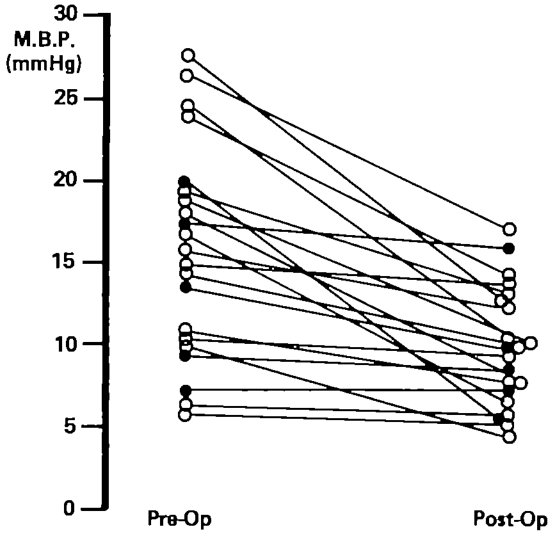

Figure 3 *Mean barrier pressure in 21 patients in whom the pressure did not increase after fundoplication:* ○, *successful operations;* ●, *failed operations*

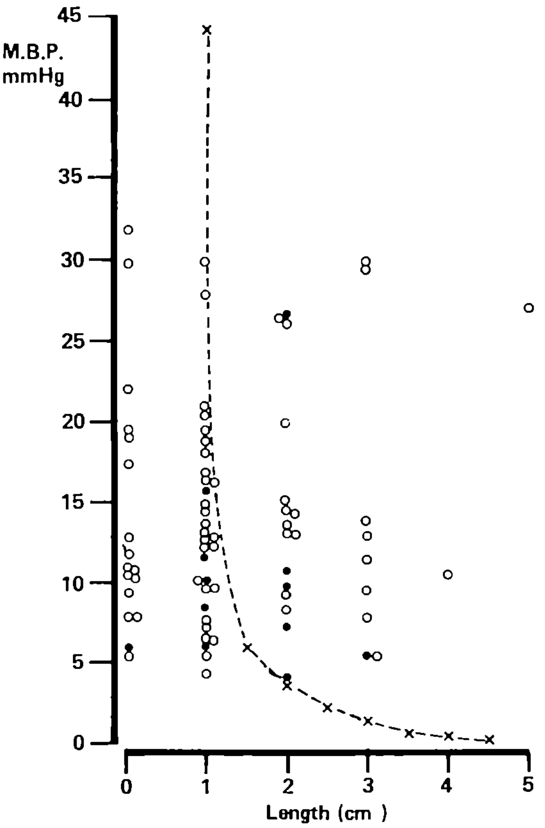

Figure 4 *Relationship between Mean barrier pressure and length in postoperative patients:* ○, *successful operations;* ●, *failed operations. Dotted line represents data from DeMeester*[7]

although this is not a difficult measurement to make. In our own study we have measured both pressure and length and have correlated the results with the success or failure of the operation. To our knowledge this comparison has not been made before in an adequate number of cases having a single anti-reflux operation. The nearest approach is that of DeMeester[1], but he looked at a very small number of patients having one of three operations (15 in each group). We do not think that such a small study can be regarded as authoritative.

After the floppy Nissen operation there was a statistically significant increase in the MBP, an observation that has been made many times before. However, 21 of our 79 patients had a decreased pressure and yet 16 (76·2 per cent) still had good reflux control demonstrated by the most accurate criteria available at this time. Donahue *et al.*[9] have similarly found a reduced pressure in 4 of 19 patients with satisfactory reflux control after floppy Nissen fundoplication. One might expect that a reduced pressure could be counteracted by an increased sphincter length, but this was not the case in our patients and 14 of 18 (77·8 per cent) with a reduced pressure and length had a good result.

We believe that there are only two possible explanations for these rather surprising results. Firstly the pre-operative values for pressure or length may have been high because of some effect of the disease. This is most unlikely to be the case for LOS pressure since experimental reflux oesophagitis has been shown to decrease LOS pressure[10], quite apart from the known tendency of a hypotensive sphincter to predispose to reflux. However, one of the manometric signs of hiatus hernia is an apparently elongated sphincter[11], and repair would therefore shorten the measured length. Only 41 (51·9 per cent) of our patients had a hiatus hernia and there was no evidence that this influenced our results.

The second possible explanation is that the pressure changes reflect an artefact of the surgical manipulation rather than being a measure of genuine physiological change. Although it is not a fashionable opinion to express we do not think that it is at serious variance with the known facts about reflux surgery. An extreme example of postoperative artefact is the patient who has oesophageal obstruction due to a 'slipped' Nissen. It is not unreasonable therefore to suggest that some of the changes that we measured were simply a consequence of surgical manipulation and altered anatomy.

Whether our results have any relevance to other operations is a matter of speculation. We suspect that measured pressure and length may be relevant in the Hill operation, but irrelevant after partial fundoplication operations and the Angelchick procedure. Only measurement of the postoperative changes in sufficiently large numbers of patients to allow comparison of successful and unsuccessful operations will clarify the matter. In the meantime over-interpretation of manometric findings should be avoided. As far as the Nissen operation is concerned reflux control must be measured directly by prolonged pH recording. It cannot be inferred from changes in the characteristics as assessed by manometry.

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Survival after resection for carcinoma of the oesophagus

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During the period 1978–1984, 525 patients referred with cancer of the oesophagus or gastro-oesophageal junction were assessed for operation and cure. After investigation, 276 patients were selected and operated upon, as a rule, 4 weeks after radiotherapy (40 Gy/4 weeks). In 224 patients (81 per cent) the oesophagus and cardia were resected and reconstructed with stomach (69 per cent), colon (21 per cent), free ileal graft (7 per cent) or Roux-en-Y-oesophagojejunostomy (3 per cent). The postresectional hospital mortality was 14 per cent in all patients and decreased to 5 per cent in 1983. Mortality was higher when the colon was used for reconstruction than when the stomach was used. By postresection staging, 82 patients were found to have stages I and II tumours and 142 patients stage III tumours. Estimated 3-year survival after resection for all male patients was 28 per cent and for all female patients was 42 per cent. Estimated 3-year survival for all patients treated for adenocarcinoma was 31 per cent. Survival was better for stages I and II patients with adenocarcinoma (52 per cent) than for stage III patients (18 per cent) (P < 0.01)*. Estimated 3-year survival for all patients treated for squamous cell carcinoma was 33 per cent. Estimated 3-year survival was better for stages I and II patients with squamous cell carcinoma (48 per cent) than for stage III patients (25 per cent)* (P < 0.001)*. It can be concluded from this study that resection of oesophagus and cardia after radiotherapy offers hope for cure in a subgroup of patients with non-advanced oesophageal cancer. The operation can be performed with acceptable mortality by experienced surgeons, especially when the stomach is used for reconstruction.*

Keywords: Oesophageal cancer, oesophageal resection and reconstruction

Carcinoma of the oesophagus and the gastro-oesophageal junction is associated with a poor survival. Many patients have disseminated disease at first presentation[1]. Those patients selected for curative treatment face an operation which is generally associated with a high postoperative morbidity and mortality[2]. Thus, only a subgroup of patients will benefit from surgery. Careful pre-operative selection, adequate adjuvant therapy, a good surgical technique and optimal perioperative care should be pursued to improve the results of treatment. In Rotterdam, a working group on oesophageal cancer has been set up, combining the workforce of the departments of general surgery, gastroenterology, ENT surgery and oncology of the University Hospital, Dijkzigt and of the departments of radiotherapy and oncology of the Rotterdam Radiotherapeutic Institute. The previous results obtained by this group were published in 1979[3]. The outcome for patients with cancer of the oesophagus or the gastro-oesophageal junction selected after pre-operative radiotherapy between 1978 and 1984 is reported.

Materials and methods

Patients

Patients were selected from 525 patients with histologically proven cancer of the oesophagus or the gastro-oesophageal junction referred to the working group on oesophageal cancer in Rotterdam between January 1978 and January 1984.

Pre-operative screening: resection and operation

Patients were found to have an incurable tumour when extension outside the oesophagus or metastatic spread was shown during investigation, which included barium studies, oesophagogastroscopy, indirect laryngoscopy in all patients and bronchoscopy and laparoscopy when indicated. Computed tomographic (CT) scanning, ultrasound and ultrasound-guided cytology were added in 1980. Suitability for operation was based on medical history, physical examination, ECG, chest X ray, pulmonary function tests and blood gas analysis. There was no upper age limit for operation.

Pre-operative radiotherapy

All patients with adenocarcinoma or squamous cell cancer were considered for pre-operative radiotherapy. Some patients with adenocarcinoma of the gastro-oesophageal junction, with limited extension into the oesophagus, underwent primary surgery with postoperative radiotherapy when this was indicated (stage III). Pre-operative radiotherapy was given with a 4–6 MV linear accelerator by means of two parallel opposed portals to a total tumour dose of 40 Gy in fractions of 2 Gy in 4 weeks. Field size extended to at least 5 cm from the upper and lower borders of the tumour and to 3–4 cm from the lateral borders. High cervical carcinomas were treated by radiotherapy alone. Re-evaluation was performed 4 weeks after 40 Gy total dose (TD) in 20 fractions over 4 weeks. When no tumour residue was found a second course of radiotherapy (30 Gy TD in 15 fractions over 3 weeks) was given. When a significant tumour residue was found, surgery was performed.

Surgery

Laparotomy and right thoracotomy and, in some patients, a right-sided cervical incision were carried out 4 weeks after the last irradiation. Incurability was determined on gross findings during operation, such as invasion outside the oesophagus in adjacent structures or distant metastases. No palliative bypass surgery was performed. When operable with no local extension, resection of the involved part of the oesophagus was carried out with 5 cm of uninvolved oesophagus proximal and distal to the tumour, when this was possible. Free margins were confirmed intra-operatively by frozen sections. Reconstruction was performed by some form of gastric tube or gastric interposition, colonic interposition

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or oesophagojejunostomy depending on the anatomical possibilities. The proximal anastomosis was situated in the right hemithorax or in the neck, depending on the site of the tumour and field of irradiation. All patients underwent a gastric drainage procedure (pyloromyotomy or pyloroplasty) and received a needle jejunostomy for early postoperative enteral feeding. High cervical and postcricoid carcinoma with significant tumour residue after radiotherapy were treated by laryngopharyngectomy and cervical oesophagectomy, followed by reconstruction by means of a free ileal graft.

Staging

Staging was performed using the postsurgical resection classification (PTNM) as developed by the American Joint Committee on Cancer (AJCC)[4].

Stage I $= T_1, N_0, M_0$
Stage II $= T_2, N_0, M_0$
Stage III $= T_3, N_0, M_0$, any T, N_1–N_3, M_0

Postoperative radiotherapy

Postoperative radiotherapy was given to most patients with stage III tumours. The irradiation was given by way of rotation or 3-field technique to a total tumour dose of 24–30 Gy in 12–15 fractions over 2·5–3 weeks.

Follow-up

All patients who underwent resection of the tumour were included in the follow-up until January 1985. Mean follow-up was 19·5 months.

Survival

Only patients treated for squamous cell carcinoma and adenocarcinoma were included in the analysis of the survival data. Survival data were estimated and plotted on actuarial basis by the method of Kaplan and Meier[5]. The Logrank test was used to compare the survival rates of subgroups of patients.

Results

Patients

Between January 1978 and January 1984, 525 patients, 389 male (74 per cent) and 136 female (26 per cent), mean age 65·2 years, with cancer of the oesophagus were referred to the working group on oesophageal cancer in Rotterdam. The tumour was situated in the upper oesophagus in 60 patients (11 per cent), midoesophagus in 269 patients (51 per cent) and distal oesophagus and gastro-oesophageal junction in 196 patients (37 per cent). A total of 278 (53 per cent) of the cancers were squamous cell carcinomas and 225 (43 per cent) were adenocarcinomas (9 per cent in Barrett and 34 per cent in otherwise normal oesophagus); 22 (4 per cent) malignant tumours were classified otherwise.

Pre-operative screening

After pre-operative screening 276 patients (53 per cent) were thought to have operable and curable tumours. The other 249 patients (47 per cent) were treated by non-surgical procedures with palliative or curative intention. The percentage of patients selected for operation after pre-operative screening increased from 44 per cent in 1978 to 60 per cent in 1983. This difference is not statistically significant (*Table 1*).

Peroperative cure

Of the 276 patients who were operated upon 52 were found to be incurable during operation (19 per cent). Thus, resection of the involved oesophagus was carried out in 224 patients (81 per cent). One hundred and sixty-four patients (73 per cent) were male and 60 patients (27 per cent) were female.

Postresection histology and staging

Of all resected oesophageal tumours ($n = 224$), 98 (44 per cent) were squamous cell cancers and 115 (51 per cent) were adenocarcinomas; 11 (5 per cent) other malignancies were resected. In 82 patients (37 per cent) stage I and II cancers were resected; in 142 patients (63 per cent) stage III tumours were resected.

Distribution of the patients

The distribution of all 525 referred patients to the various groups is given in *Table 1*. Fifty-three per cent of all referred patients underwent an operation. During operation in 52 patients the tumour was found to be incurable. Thus 43 per cent (224) of all patients underwent resection. This percentage did not change significantly over the period of investigation (*Table 1*). Sixteen per cent (82) of all patients underwent a resection for tumours of stages I and II, whereas in 27 per cent (142) the resection was carried out for stage III tumours.

Reconstruction

The stomach or part of the stomach was used for reconstruction in 154 patients (69 per cent), a colonic segment in 47 patients (21 per cent), a free ileal graft in 15 patients (7 per cent), and an oesophagojejunostomy Roux-en-Y was performed in 8 patients (3 per cent).

Postoperative mortality

Of 276 patients operated upon in the study period, 32 (12 per cent) died postoperatively in the hospital. In 16 patients, postoperative mortality was the result of dehiscence of the anastomosis, leading to mediastinitis. In 11 patients respiratory complications and in 5 patients cardiovascular complications led to postoperative death. Postoperative mortality after resection with the stomach was 10 per cent (15/154), after oesophagojejunostomy 38 per cent (3/8), after free ileal grafting 0, and after use of a segment of colon 30 per cent (14/47). Colonic interposition was performed when previous gastric surgery precluded use of the stomach as a substitute. No patients died as a result of the exploratory laparotomy and/or thoracotomy. Postoperative mortality, postresectional mortality and the number of operations and resections/reconstruction per year, as well as peroperative irresectability, are given in *Table 1*. Postresectional mortality decreased from 33 per cent (6/18) in 1978 to 5 per cent (3/61) in 1983.

Survival

Survival of patients treated for adenocarcinoma ($n = 115$) and squamous cell carcinomas ($n = 98$) was studied. Postoperative mortality is included in the survival data. Survival curves, according to histology and stage, are given in *Figures 1, 2* and *3*.

Table 1 *Number and percentage of referred patients, operated patients, resectability, postoperative and postresectional mortality (1978–1984)*

Year	1978	1979	1980	1981	1982	1983/4	Total
Referred	55	67	71	101	110	121	525
Operated (%)	24 (44)	31 (46)	37 (52)	50 (50)	62 (56)	72 (60)	276 (53)
Resected + reconstruction (%)	18 (33)	24 (36)	33 (46)	38 (38)	50 (45)	61 (50)	224 (43)
Postoperative mortality (%)	6/24 (25)	5/31 (16)	6/37 (16)	5/50 (10)	7/62 (11)	3/72 (4)	32/276 (12)
Postresectional mortality (%)	6/18 (33)	5/24 (21)	6/33 (18)	5/38 (13)	7/50 (14)	3/61 (5)	32/224 (14)

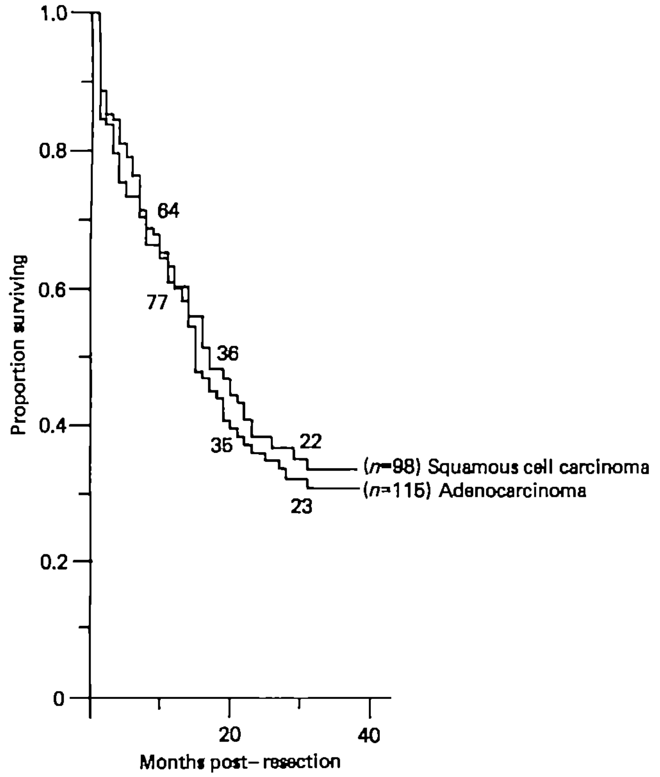

Figure 1 *Survival curve for 115 patients with adenocarcinoma and 98 patients with squamous cell carcinoma, after oesophagectomy*

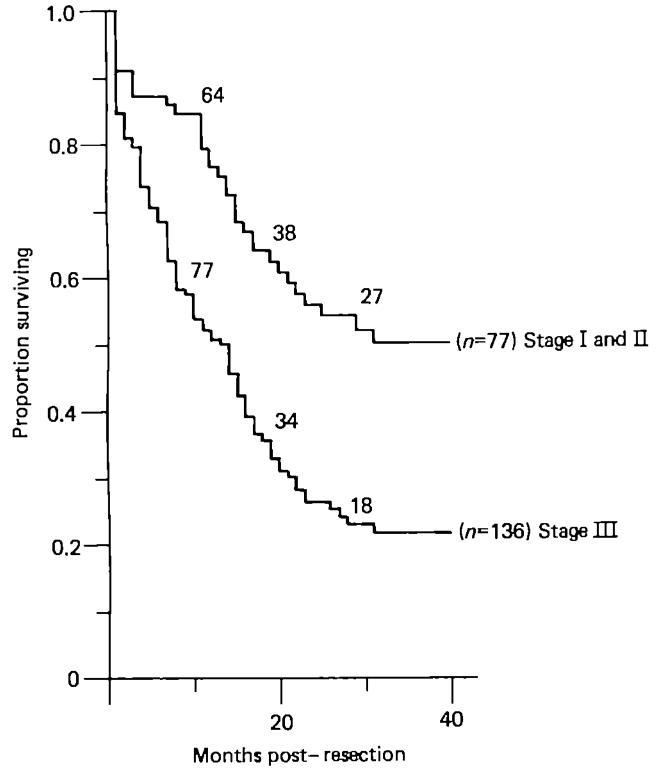

Figure 2 *Survival curve for 77 patients with stages I and II and 136 patients with stage III squamous cell carcinoma and adenocarcinoma of the oesophagus, after oesophagectomy*

Survival of the 11 patients with miscellaneous malignancies of the oesophagus was not studied. For all patients with adenocarcinoma the estimated 3-year survival was 31 per cent. For all patients with squamous cell carcinoma the estimated 3 year survival was 33 per cent (*Figure 1*). For patients treated for stage I and II tumours the estimated 3-year survival was 52 per cent. The corresponding statistic for patients treated for stage III tumours was 21 per cent. The difference was statistically significant ($P < 0{\cdot}001$) (*Figure 2*). Survival of patients treated for stage I and II adenocarcinoma was significantly longer than for stage III (3-year survival 52 per cent *versus* 18 per cent, $P < 0{\cdot}001$ (*Figure 3*). Survival of patients treated for stages I and II squamous cell carcinoma was significantly longer than for stage III (3-year survival 48 per cent *versus* 25 per cent, $P < 0{\cdot}001$) (*Figure 3*).

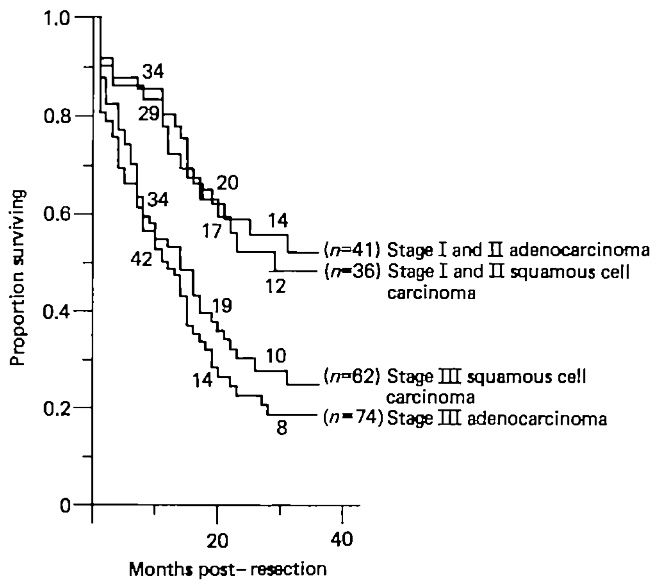

Figure 3 *Survival curve for 41 patients with stages I and II adenocarcinoma, 36 patients with stages I and II squamous cell carcinoma, 74 patients with stage III adenocarcinoma and 62 patients with stage III squamous cell carcinoma, after oesophagectomy*

For female patients estimated 3-year survival was 42 per cent and for male patients estimated 3-year survival was 28 per cent.

Discussion

Only a subgroup of all patients treated for oesophageal cancer can have hope of cure. Our efforts should be directed to better selection of patients in order to prevent unnecessary extensive surgery. Minor procedures should be pursued to increase the quality of life for patients with incurable disease. Although most authors agree with these aims, many papers on oesophageal cancer, including the present one, focus on the small group that may benefit from extensive treatment. In the working group on oesophageal cancer in Rotterdam, all 525 patients with cancer of the oesophagus and gastro-oesophageal junction referred to the group during the period 1978 to 1984 were screened for cure and operation. Only 53 per cent of these patients were thought to be operable and curable and 43 per cent were found to be curable during laparotomy and/or thoracotomy. Despite the introduction of CT scanning this percentage did not alter.

Although the results of a recent prospective randomized trial on the effect of pre-operative radiation are not in favour of this therapy[6], this modality has been advocated by others[7,8], and has been used by our group with an acceptable morbidity[3]. In the patients who have had pre-operative radiotherapy the postsurgical resection classification showed a similar distribution of stages of tumour to that of Ellis *et al.* who did not give pre-operative radiotherapy[9]. Thus, alteration of the stage of the tumour by radiotherapy, as reported for rectal cancer, is unlikely for oesophageal cancer, despite striking changes in individual patients.

Postoperative or hospital mortality for oesophageal resection and reconstruction can be as high as 30 per cent[2]. Postoperative mortality was 12 per cent and postresectional mortality was 14 per cent for our patients with a decrease in the latter to 5 per cent in the last year of the study. Greater experience in the treatment of patients with oesophageal cancer leads to reduction in postoperative mortality, as reported in studies from other centres treating large numbers of patients[10]. It is possible that other techniques, such as oesophageal resection without thoracotomy, could further lower the postoperative mortality[11,12]. The use of the stomach for reconstruction after oesophagectomy is favoured because of the low operative mortality[11–13]. However, after previous gastric surgery colon interposition is required despite the high postoperative mortality.

The use of a free segment of small bowel with vascular anastomoses in the neck for reconstruction after resection of the larynx, pharynx and the cervical oesophagus was safe and successful in all 15 patients in whom this procedure was undertaken[14]. Dehiscence of the proximal anastomosis and mediastinitis, a complication feared for its mortality, was infrequently seen in this series. In all patients, oesophagectomy was performed using a right-sided thoracotomy. Resection with intention to cure was carried out in all patients without lymph node dissection, as advocated by Skinner[15]. No palliative resection or bypass was performed. According to the postsurgical staging, 37 per cent of the patients had tumours removed that were confined to the oesophagus (stages I and II). Most patients (67 per cent) had positive regional lymph nodes or infiltration through the wall of the oesophagus (stage III). As expected, 3-year survival was significantly better for patients with stage I and II tumours (48 per cent) for squamous cell cancer and 52 per cent for adenocarcinoma) than for stage III tumours (25 per cent and 18 per cent). Our results compare well with the data in the literature.

En bloc resection, as carried out by Skinner, did not improve survival[15]. Orringer reported on 100 patients treated by transhiatal oesophagectomy without thoracotomy, a method that makes *en bloc* resection impossible. No radiotherapy was given to these patients. Fifteen patients were assigned to stage I and II, and 68 to stage III. Two-year survival in stage I and II was 54 per cent and in stage III 28 per cent[11]. The similarity of the survival data to the data presented in this study is striking. It seems unlikely that radiotherapy as in this study, or lymph node dissection as carried out by Skinner *et al.*, contribute much to survival in patients with oesophageal cancer. Adjuvant chemotherapy may be used on a wider scale in the future[16,17]. To date there is no evidence that this therapy is effective.

The quality of life has not been evaluated in great detail in the present study; it was our opinion that patients surviving longer than 6 months after resection (i.e. 80 per cent of the female and 70 per cent of the male patients) had a good quality of life. Others have found no diminished quality of life after resection and reconstruction for oesophageal cancer when no recurrence occurred within one year[18].

Since resection is such a formidable procedure and complete recovery will take at least a few months, proper selection of patients in good condition with curable disease, optimal patient care during the various phases of treatment, good surgical technique and postoperative care are of utmost importance. For those patients who are not selected for curative treatment, the best palliative (non-surgical) treatment should be used.

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Dietary habits of patients with regurgitation after colon interposition

The dietary habits after colon interposition following oesophagectomy in patients without symptoms ($n = 8$), *with regurgitation* ($n = 22$) *and in sex- and age-matched healthy controls* ($n = 20$) *were studied by a 7-day diary method. The patients ate smaller meals* (*1080* ± *90 kJ* versus *1810* ± *151 for the controls*, $P < 0{\cdot}01$), *more frequently during the day* (*eight* versus *five in the controls*). *Solid and sour foods were preferred, especially by those with regurgitation, compared with controls. The asymptomatic patients consumed more milk and coffee and less cheese, sour milk, meat, fish, eggs, tea and orange juice than the patients with regurgitation. Vegetable fats and medium chain triglycerides were consumed in negligible amounts. The patients with regurgitation had more fluids separately from meals than the asymptomatic patients. The results suggest that intake of vitamin supplements and replacement of animal fats by vegetable fats may be useful in these patients. Much of the dietary difficulties after colon interposition might be the result of the intra-abdominal colon graft loop anastomosed to the antrum; a short graft with a more proximal anastomosis to the lesser curvature merits study in this context.*

Keywords: Colon interposition, dietary habits, food intake, energy, nutrients, regurgitation

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Regurgitation and the inability to lie flat after meals are distressing symptoms after colon interposition, a procedure used to restore contuity after oesophageal resection[1–5]. Colon interposition is usually accompanied by truncal vagotomy and pyloroplasty. After the procedure, food is conducted mainly by gravity into an atonic stomach which has a reduced capacity for acid secretion and is subject to bile reflux. It might be expected that regurgitation would be associated with changes in diet and nutrition. However, there are contradictory data regarding the effects of colon interposition on the growth of children[4,6]. Further, there are studies which show that adult patients have impaired nutrition after colon interposition, and it is suggested that this is a consequence of malabsorption (Reference 7; E. Harju and J. Isolauri, unpublished results). However, earlier reports have not paid much attention to the dietary habits of these patients. Thus it was felt that the evaluation of this question in patients with and without regurgitation after colon interposition and in healthy controls would be of interest.

Patients and methods

During a 22-year period (between the years 1964 and 1985) 250 patients with oesophageal carcinoma and 60 with benign oesophageal disease had undergone colon interposition in Tampere University Central Hospital, Finland, (References 8–10, E. Harju and J. Isolauri, and J. Isolauri, M. O. Koskinen, L. Pöyhönen, A. Uusitalo, H. Markkula, unpublished results). All patients ($n = 32$) available for review with benign disease alive between May and September 1985 were incorporated into the study group; an oesophageal stricture had resulted from alkali ingestion in 17 patients, from other corrosive agents (glacial acetic acid) in 2 and from reflux oesophagitis in 8 patients. Other benign oesophageal diseases causing resection in five patients included one patient with a stricture following spontaneous rupture of the oesophagus and four patients with a stricture of unknown cause (possibly corrosive trauma in childhood or due to reflux oesophagitis). To minimize the effect of carcinoma growth, only patients ($n = 12$) operated >2 years previously for oesophageal squamous cell carcinoma were chosen for the study.

Thus 44 patients, 21 men and 23 women, with a mean age at operation of 54 years, were studied. The present follow up was performed at an average of 68 months after operation; the interval was <24, 24–60, 61–120 and >121 months in 7, 14, 15 and 8 patients respectively. The left colon was selected for interposition in 30 patients; the right colon and transverse colon in 9 and 5 patients respectively. There were 28 antiperistaltic and 16 isoperistaltic colon grafts.

In various studies of these patients no significant differences were detected between those with antiperistaltic grafts and those with isoperistaltic colon grafts,(References 8–10, E. Harju and J. Isolauri, and J. Isolauri, M. O. Koskinen, L. Pöyhönen, A. Uusitalo, H. Markkula, unpublished results). The lower end of the interposed colon was connected to the anterior surface of the gastric antrum. Truncal vagotomy was always part of the operation and a pyloroplasty had been performed in each case. All the operations except four were performed in one stage. The posterior mediastinum and retrosternal route were used for the colon graft in 39 and 5 patients respectively. The operation was performed without a thoracotomy on 34 occasions.

The dietary habits were studied by a 7-day diary method which noted the time of eating, the amount and quality of the food and fluids consumed, and the symptoms experienced. This food recording method has been applied to more than 2000 subjects and has been controlled in several ways[11–14].

Among the 44 patients there were 8 asymptomatic patients and 22 patients with regurgitation, including 3 patients with severe symptoms of regurgitation, vomiting and cough[8]. The patients with regurgitation reported that they suffered from a regular daily spontaneous flow of gastric content back into their mouth. This was confirmed by the 7-day diary. The asymptomatic patients did not report any symptoms. Sex- and age-matched healthy subjects ($n = 20$) formed the control group for dietary studies (*Table 1*).

In most patients, body weight had decreased in the immediate postoperative period and then remained constant at the new level. A decrease was more common in the patients with regurgitation (18 of 22) than in those without symptoms (2 of 8). However, the mean values of the present body weights (57 ± 7 and 56 ± 6 kg) and the mean values of the postoperative weight losses (4 ± 3 and 5 ± 4 kg) were practically the same in the patients with regurgitation and those without symptoms.

Results

The patients with regurgitation had a different diet from the patients without symptoms after colon interposition (*Table 2*). The patients with regurgitation tended to restrict the amount of fluids during meals and liked to ingest sour food. The asymptomatic patients consumed more milk than the patients with regurgitation, and, in fact, consumed as much of this as the controls. Other dairy products, e.g. cheese and sour milk, were consumed in higher ($P<0\cdot05$) amounts by the patients with regurgitation than by those without symptoms. Both groups of patients drank more sour milk than the controls ($P<0\cdot05$). Patients with antiperistaltic or isoperistaltic colon grafts did not show any significant differences.

The colon interposition patients consumed low amounts of vegetable fats, as did the controls (*Table 2*).

The tendency to avoid fluids with meals was combined with a higher ($P<0\cdot05$) consumption of solid food, e.g. meat, fish and eggs, in patients with regurgitation when compared to those without symptoms. The patients with the most severe regurgitation consumed the highest amounts of meat, fish and eggs, namely 135 ± 15, 55 ± 25 and 68 ± 27 g daily, respectively; fish was consumed more by symptomatic patients than by the controls.

The patients with regurgitation and those without symptoms drank equal amounts of coffee and tea when calculated together, but an increase of symptoms was associated with tea drinking in conjunction with a reduction in coffee consumption. The asymptomatic patients drank more tea than the controls, but drank coffee in equal amounts. The patients with regurgitation showed a higher ($P<0\cdot05$) daily consumption of orange juice than the asymptomatic patients and controls (an almost fourfold difference).

The intake of energy was slightly lower in patients after colon interposition than in controls, but the intakes of symptomatic and asymptomatic patients were very similar to each other (*Table 2*). The difference in food consumption meant that the patients with regurgitation received slightly more dietary protein and niacin, and significantly more ascorbic acid than the asymptomatic patients. The patients after interposition ingested less vitamin A than the controls, those with regurgitation having the lowest vitamin A intake.

The meals of the patients after colon interposition were small and contained significantly ($P<0\cdot01$) less energy than those of the controls (1080 ± 90 kJ and 1810 ± 151 kJ respectively). Both the patients without symptoms and those with regurgitation had a higher number of daily meals (median of eight) than the controls (median of five).

Table 1 *Comparison of patients with colon interposition and healthy controls*

	Patients with regurgitation	Patients without symptoms	Control group (healthy)
Mean age (years)	58 ± 14	59 ± 15	57 ± 16
Number of men	4	10	10
Number of women	4	12	10
Body weight (kg)	57 ± 7	56 ± 6	64 ± 8

Discussion

There are four principal categories of oesophageal reconstruction: colon interposition, jejunal interposition, gastric tubes and oesophagogastrostomy. In experimental work most motor activity has been found in jejunal interposition. Colon interposition grafts exhibit some motor response to an acid stimulus, but the gastric tube is totally inactive[15]. Oesophagogastrostomy has the highest incidence of regurgitation. Technical difficulties in jejunal interposition are frequent due to the short vascular pedicle[16], while construction of a gastric tube is technically very demanding[17]. Furthermore, gastric tubes and oesophagogastrostomy are prone to stricture, a complication which was usually the primary indication for the interposition. Thus we consider colon interposition and oesophagogastrostomy as the procedures to be used in oesophageal reconstruction.

The present study suggests that after colon interposition patients have different dietary habits to controls, and that patients with regurgitation have different habits when compared with asymptomatic patients. After colon interposition patients eat food or drink fluids in small amounts, taken frequently at short intervals.

The features of the diet of patients with regurgitation are the high amounts of solid and sour food (e.g. meat, sour milk and orange juice), and the tendency to drink fluid separately rather than with solid food. The need for such a diet is obvious when regurgitation occurs through an interposed colon graft which serves mostly as a passive conduit for food and fluids. Furthermore, vagotomy with pyloroplasty may lead to a drastic reduction in gastric acid secretion and predispose to bile reflux. It is not actually known how much the capacity of acid secretion is decreased or what is the value of the pH level of gastric content after colon interposition. We have been unable to pass a pH detector into the stomach of these patients. Scintigraphic studies have shown duodenogastric reflux in 16 and a duodenogastrocolic reflux in 8 of 20 of our colon interposition patients[11]. Thus the present dietary findings may be signs of adaptation to reduce the alkaline and bile taste of regurgitation.

Table 2 *The mean daily intake of food (g) energy and nutrients by patients after colon interposition and by the controls*

	Asymptomatic ($n=8$)	Regurgitation ($n=22$)	Control ($n=20$)
Vegetable fats	7 ± 3	4 ± 2	8 ± 4
Dairy products	684 ± 76	512 ± 53	701 ± 72
Milk	572 ± 86	361 ± 44	571 ± 61
Cheese	13 ± 8	22 ± 4	24 ± 6
Sour milk	76 ± 24	106 ± 22	49 ± 13
Butter	23 ± 6	24 ± 4	25 ± 5
Meat*	72 ± 12	92 ± 10	132 ± 13
Fish*	10 ± 4	46 ± 7	16 ± 5
Eggs*	12 ± 3	31 ± 6	39 ± 7
Coffee	423 ± 50	339 ± 47	410 ± 51
Tea	61 ± 59	119 ± 32	23 ± 16
Other fluids, mostly orange juice	63 ± 28	239 ± 67	71 ± 34
Energy (kJ)	8639 ± 897	8562 ± 564	9051 ± 637
Protein (g)	64 ± 7	77 ± 5	72 ± 6
Fat (g)	89 ± 8	84 ± 7	94 ± 9
Carbohydrates (g)	273 ± 36	260 ± 18	262 ± 21
Vitamin A (μg retinol)	981 ± 271	760 ± 70	1351 ± 311
Thiamine (mg)	1·3 ± 0·15	1·3 ± 0·12	1·4 ± 0·13
Riboflavin (mg)	2·2 ± 0·27	2·1 ± 0·17	2·4 ± 0·25
Niacin (mg)	22 ± 2·7	28 ± 2·2	31 ± 3·2
Ascorbic acid (mg)	66 ± 12	89 ± 8	95 ± 14

*Meat, fish and eggs were consumed by the patients with severe regurgitation in amounts of 135 ± 15, 55 ± 25 and 68 ± 27 g respectively

The differences in fluid and food consumption resulted in differences in energy and nutrient intakes which were below the control values for several vitamins. The most obvious differences between symptomatic and asymptomatic patients were in the intakes of vitamin A and ascorbic acid. These are explained by the higher consumption of milk and orange juice by the respective groups. In some patients after colon interposition, vitamin supplements would be the best method of increasing their nutrient intakes.

Most of the present patients lost weight after operation. Vagotomy has been associated with weight reduction[18], but not so frequently or as rapidly as seen after colon interposition. Thus one mechanism for the weight loss is a low daily energy intake. On the other hand, the present patients did not have a clinically obvious fat malabsorption with diarrhoea, as suggested earlier[7]. However, occult fat malabsorption may contribute to the low body weight. The weight might be increased by consumption of medium chain triglycerides, which are known to be absorbed despite malabsorption of other fats and which also increase the absorption of these other fats[7].

Experiments on dogs have shown that gastric tubes have a higher intrinsic pressure barrier than colonic tubes. A 2·5–6 cm segment prevents reflux and the tube maintains a pressure barrier 10 cmH_2O higher than stomach pressure, whereas colonic segments require 12 cm of subdiaphragmatic length to control reflux and maintain a pressure barrier only 2 cmH_2O above gastric pressure[19]. Furthermore, radionucleotide tests have shown rapid gastric emptying and a reservoir function of the intra-abdominal part of colon grafts in our patients[10]. Thus the patients have to regulate their eating so that there is a balance between the tendency to regurgitate and the rapid gastric emptying with dumping. It seems that the asymptomatic patients have found this balance, but at the cost of a normal diet. In order to reduce the regurgitation symptoms we suggest that a more proximal anastomosis, to the lesser curvature with a short intra-abdominal graft, may be of value. Further clinical studies to define the effects of different lengths of intra-abdominal colon loop on reflux are needed.

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Parenteral nutrition in the surgical patient

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Surgeons who early in their careers realize the impact of malnutrition on the success of their clinical endeavours have always been leaders in the evolution of aggressive nutritional care[1]. Intravenous therapy has evolved from the infusion of dextrose introduced at the turn of the century through the use of fat after World War I, casein hydrolysates in 1931[2], amino acids in 1940[3], lipid emulsions in 1961[4], and hypertonic dextrose in 1968[5].

Safe total parenteral nutrition (TPN) was achieved with fat emulsions in Europe in the early 1960s[6]. In 1968, Dudrick *et al.* described growth, development and positive nitrogen balance in laboratory and clinical studies by employing long-term parenteral nutrition with hypertonic dextrose, fibrin hydrolysates, vitamins and minerals[5]. Since then, the field of parenteral nutrition has progressed through varying phases into the present state of safe, effective TPN with three-in-one solutions (administering fat, protein and carbohydrates in one bag). Nevertheless, it should be emphasized that the best route for satisfying nutritional needs is the gastrointestinal tract, and parenteral alimentation becomes necessary only when the gut is unavailable for long periods[5].

Nutritional assessment

The object of nutritional assessment (*Table 1*) is to detect and categorize patients with different types and degrees of malnutrition and relate these to the risk of morbidity and mortality. In one survey carried out by Bistrian *et al.* approximately 50 per cent of patients in the surgical ward of a district general hospital were moderately to severely malnourished[7]. A detailed history, including dietary history, and physical examination are the first steps in nutritional assessment. Variables most commonly used to relate nutritional status to postoperative complications include[8–14] absolute weight loss of more than 10 per cent in the last 6 months, serum albumin of less than 35 g l^{-1} and a total lymphocyte count of less than 1500 mm^{-3}. Other variables commonly used include anthropometry of the arm, creatinine height index, hand grip dynamometry, serum transferrin and delayed hypersensitivity reponse to common skin antigens[11,14–16]. Body cell mass (BCM) represents metabolically active, potassium rich cells responsible for O_2 consumption. As potassium is almost entirely intracellular, total body potassium measurement may be used as an index of BCM[17]. Techniques such as ^{40}K or ^{42}K dilution, and the indirect method of ^{24}Na dilution have been developed for this purpose[18–20]. Similarly, total body nitrogen, and, thus, the lean tissue can be measured by *in vivo* neutron activation analysis[21]. These sophisticated research techniques are not widely available and, except for ^{40}K, involve some radiation[14]. As they are relatively more accurate, they could be more widely employed to validate the parameters commonly used for nutritional assessment[14].

Harvey *et al.* devised a hospital prognostic index employing different variables to predict subsequent mortality[12]. Similarly, Buzby *et al.* formulated the prognostic nutritional index, a linear predictive model using various nutritional and biological parameters[22]. Buzby's group demonstrated that, if the index was >50 per cent, the patient had an increased risk of infective and other postoperative complications. In another phase of the same study, it was demonstrated that administering pre-operative TPN for at least 7 days to the high risk group reduced complications[23]. It is uncertain how much the components of these indices relate to nutritional status, as they are affected by many other factors (*Table 1*). There is also a need for a more precise classification of risk factors such as infection and postoperative complications[14]. A recent study indicated that a careful assessment of medical risk, noting cardiorespiratory disease and pre-existing sepsis as well as nutritional state, is as effective as any other currently used indicator of risk[24].

Energy requirements

The term hyperalimentation means intravenous administration of nutrients substantially in excess of current requirements[25]. Although this term is still commonly used, it is really a misnomer as the emphasis is no longer on overfeeding the patient. Caloric supply (particularly in the form of glucose), which greatly exceeds actual energy expenditure, can foster hepatic lipogenesis and hepatic dysfunction[26,27] and increase O_2 consumption and CO_2 production.

Ideally, caloric requirements should be calculated by actual measurement, of the resting energy expenditure[28,29]. The Horizon Metabolic cart (Beckman Instruments, Schiller Park, Illinois, USA) is a useful mobile instrument with O_2 and CO_2 sensors which employs the principle of indirect calorimetry. It is particularly useful in critically ill and septic patients whose energy needs cannot otherwise by precisely predicted[30]. In practice, basal energy ependiture is predicted by the Harris–Benedict formula[31], and appropriate adjustments are made for the degree of stress and activity in calculating total energy expenditure[32,33]. Even if a patient is in severe hypermetabolism with major burns, energy needs will not exceed 200 per cent of the predicted basal energy expenditure[33,34]. So, if an adult patient resting in bed for elective surgery[35] needs 25 kcal kg^{-1} day^{-1}, one with severe burns will need 50 kcal kg^{-1} day^{-1}. Patients with varying degrees of stress will be within the range usually of 30–40 kcal kg^{-1} day^{-1}. Calculation of total energy expenditure in hospitalized patients is summarized in *Table 2.*

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Table 1 *Nutritional assessment*

		Malnutrition			
Body compartment	Measurement	Mild	Moderate	Severe	Comments
Total body mass (lean, fat, water)	Percentage of actual weight lost in last 6 months	5–10%	10–20%	>20%	Altered by oedema, ascites, and tumour
Fat	Triceps skinfold thickness (TSF)	—	—	<5th percentile	Anthropometry altered by fluid status, and observer-dependent
Skeletal muscle	Mild arm muscle circumference = (mid arm circumference $-\pi$TSF)	—	—	<5th percentile	—
	Creatinine height index = $\left(\frac{\text{Actual 24 h urinary creatinine} \times 100}{\text{Ideal urinary creatinine for height}}\right)$	80–90%	60–80%	<60%	Accurate 24 h urine collections are difficult
Visceral proteins	Serum albumin	28–35 g l^{-1}	21–28 g l^{-1}	<21 g l^{-1}	Altered in liver disease, enteropathy, nephrotic syndrome, and metabolic stress
	Serum transferrin	1·5–2 g l^{-1}	1–1·5 g l^{-1}	<1 g l^{-1}	Altered in iron deficiency anaemia, chronic renal failure, and metabolic stress
Immune competence	Total lymphocyte count	1200–1500 mm^{-3}	1200–800 mm^{-3}	<800 mm^{-3}	Immune competence may be affected by steroids, chemotherapy, or general anaesthesia
	Delayed hypersensitivity to common skin antigens at 24–72 h	Reactive	Partially reactive	Anergic	—

Compiled from References 8, 9, 11, 16

Table 2 *Determination of energy requirements*

1. Basal energy expenditure (BEE)
   BEE in men = 66·47 + 13·75W + 5H − 6·76A
   BEE in women = 655·1 + 9·56W + 1·85H − 4·68A
   W, weight in kg; H, height in cm; A, age in years
2. Stress factor (correction factor for the degree of stress)

Mild starvation	0·85–1·00
Postoperative (no complication)	1·00–1·05
Peritonitis	1·05–1·25
Severe infection	1·30–1·55
Cancer	1·10–1·45

3. Activity factor = 1·25 for ambulatory patients
4. Total energy expenditure = BEE x stress factor x activity factor

Compiled from References 31, 32, 36

Body fuels

The concept of using both fat and carbohydrate for non-protein calories was evolved to minimize the complications accompanying the excessive administration of glucose calories alone[30] as well as offering the benefits of fat emulsions[27].

Glucose

This is an essential substrate for brain, red blood cells and renal medulla, and is a source of energy even in the absence of oxygen (anaerobic glycolysis), which may be important in pathological conditions such as cardiac ischaemia. Glucose provides 4 kcal g^{-1} of anhydrous glucose, and utilization is optimum when it is administered at a rate of 4–5 mg kg^{-1} min^{-1} (Reference 37). Administration in excess of 7 mg kg^{-1} min^{-1}, even with insulin, may only enhance the glucose clearance rate without affecting oxidation rate[37]. It is our practice not to give more than 300–400 g day^{-1} of dextrose in a 70 kg adult.

Xylitol

This is a five-carbon polyol which yields 4·06 kcal g^{-1}. It reduces gluconeogenesis, moderates blood glucose and insulin elevations, and also promotes fatty acid oxidation and mobilization of endogenous fat[38,39]. It is still under investigation in the United States but shows promise as a caloric source in diabetics and critically ill patients[38]. A mixture of 30 per cent xylitol and 70 per cent glucose has been employed in clinical studies. The margin of safety of xylitol is substantially less than with glucose, and large amounts may be toxic[38].

Standard, synthetic amino acid solutions

These solutions contain a mixture of essential and nonessential amino acids providing 4 kcal^{-1} g^{-1}. A non-stressed patient needs 250 mg nitrogen kg^{-1} day^{-1} (1 g nitrogen = 6.25 g protein), while a stressed patient may need up to 400 mg kg^{-1} day^{-1} (Reference 35). Leucine, isoleucine and valine are the branched chain amino acids. They are uniquely oxidized in the skeletal muscle and adipose tissues and increase hepatic protein synthesis[40,41] and reduce postinjury catabolism[42,43]. Improved nitrogen balance has also been shown in a dose-related fashion in hypercatabolic patients[44]. Extrapolating these results, a case could be made for administering branched chain amino acids in stressed patients when protein load is restricted for reasons such as uraemia. However, it should be emphasized that branched chain amino acids are administered as a mixture of essential and nonessential amino acids enriched up to 50 per cent with branched chain amino acids.

Lipid emulsions

These are mainly polyunsaturated long chain triglycerides. They are isotonic, can be administered peripherally and have a caloric value of 9 kcal g^{-1} and provide essential fatty acids. There is evidence that emulsions in excess of 50 per cent of calories, under certain conditions, can cause impaired bacterial clearance and compromise neutrophil and reticulo-endothelial system function[45]. Therefore, it is our practice to limit lipid provided as long chain triglycerides to a maximum of 1·5 g kg^{-1} body weight or 100 g day^{-1} for a 70 kg adult.

Medium chain triglycerides

These are esters of saturated fatty acids with chain lengths of 6–12 carbon atoms. These are now commercially available only in some parts of Europe. They simply 8·1 kcal g^{-1}, are as nitrogen sparing as long chain triglycerides and do not need carnitine for metabolism (β-oxidation). Medium chain triglyceride emulsions do not seem to block reticulo-endothelial system function[45] and show a great promise as a caloric source in septic and traumatized patients. However, it is to be emphasized that medium chain triglycerides do not contain significant amounts of essential fatty acids. Therefore, a mixture of medium and long chain triglycerides and LCT is commonly used.

Mixing considerations

Stock solutions of lipid, (Soybean emulsion 10 and 20 per cent) amino acids (10 per cent) and dextrose (70 per cent solution) may be combined to form a three-in-one solution of appropriate concentrations within the defined volume. Three-in-one solutions are easy to administer, reduce the need for nursing supervision and reduce the risk of infection inherent in 'piggybacking' lipid emulsions. Mixing is carried out in the pharmacy under sterile conditions within a laminar flow hood. We use an Automix high-speed computerized compounder, (Travenol Laboratories Inc., Deerfield, Illinois, USA) which also assists in patient data entry, solution calculations, label preparation and fast accurate mixing. Lipid should be mixed with the amino acid solution before mixing with acidic dextrose solutions, cations, and other additives. Whenever lipid is used, bags made of ethylene vinyl acetate should be used instead of polyvinyl chloride containers to prevent lipid–container interaction[46].

Electrolytes, vitamins, and trace elements can safely be added to the TPN solution in reasonable therapeutic quantities[47]. If needed, some drugs including heparin[48], cimetidine[49], hydrocortisone[47,50], albumin[51], hydrochloric acid (not to be added with lipid emulsion)[47,52], iron dextran[53], aminophylline[47] and insulin (half of which will be adsorbed on to the bag and tubings)[54] can safely be added to the TPN solution. If absolutely necessary, most of the antibiotics can be piggybacked directly into the TPN line. Amphotericin and vancomycin are examples of drugs that are generally incompatible with TPN solutions[50,55,56].

Peripheral intravenous nutrition

Protein-sparing therapy is the provision of standard crystalline amino acid solutions through a peripheral intravenous line providing 1.0–1.5 g protein per kg body weight without supplemental fat or dextrose[57,58]. In a moderately stressed, well-nourished patient and, if adequate oral intake is anticipated in 5–7 days, protein-sparing therapy is recommended. This will improve protein synthesis and minimizes skeletal muscle catabolism[57–60]. Hypocaloric amounts of amino acids are also extremely useful in obese patients, particularly Type II diabetics, to minimize hyperglycaemia and hyperinsulinaemia, mobilize fat stores and enhance synthesis of ketone bodies which are used as an energy source, sparing body protein[61].

By using fat emulsions to provide 30 to 60 per cent of caloric input, full energy and protein needs can be met through a peripheral vein[62,63]. Solutions with an osmolality greater than 600 mmol/l or with potassium concentrations greater than 60 mmol/l are more likely to cause phlebitis[64]. Therefore, total peripheral nutrition requires a larger fluid volume than with central venous feeding. The advantages of fat emulsions are that they have high caloric density, particularly the 20 per cent lipid emulsions[65] and spare nitrogen as well as dextrose in the presence of amino acids[66].

The risk of phlebitis may be minimized by adding 1000 units of heparin and 5 mg of hydrocortisone to each litre of solution[63]. However, protein-sparing therapy is not indicated in patients who are severely stressed, and total peripheral nutrition is less applicable in patients who need complete nutritional replacement or fluid restriction or in those with inadequate peripheral venous access.

Central TPN

If the patient is a candidate for complete nutritional replacement and gastrointestinal function is uncertain, it is in the patient's best interest to insert a central line early and start TPN. Hypertonicity of the TPN solution necessitates its delivery into the superior vena cava. The large diameter and increased volume of blood flow facilitates rapid dilution and peripheral distribution of the nutrients at isotonic concentrations[5]. The superior vena cava may be cannulated by percutaneous puncture of the subclavian, internal jugular or external jugular veins. Infraclavicular puncture of the subclavian vein is the most commonly used approach[67]. It is acceptably safe, and the catheter exit site is easy to manage and more comfortable for the patient. Internal jugular vein puncture may be preferred in severely wasted, emphysematous patients on ventilators as they run a greater risk of pneumothorax[68,69]. Any difficulty with the exit site in this approach may be solved by creating a tunnel and bringing the catheter out through the anterior chest wall[68]. Cannulation of the superior vena cava by peripheral cut-down is probably indicated in patients with coagulopathy, although this approach does not seem to lessen the complication rate[67].

It is very important that insertion and maintenance of central access should carry minimal complications. *Table 3* compares complication rates of a team of experienced personnel with that of individual physicians[70]. Experience with at least 50 central line insertions is necessary before the complication rate is reduced to nearly zero[71,72], and junior staff must be closely supervised[72].

Silastic catheters reduce, but do not eradicate, the risk of venous thrombosis. Addition of 6000 units of heparin per day to TPN solutions reduces the risk from 5·4 per cent to <1·2 per cent[73]. A major complication during maintenance is catheter sepsis. This may be due to catheter seeding by the organisms in the blood, entry of organisms through catheter exit site, colonization of the catheter hub, or contamination of the infusate[74]. Tunnelling of the catheter does not reduce sepsis[75], although there are uncontrolled data which suggest the contrary[76]. Heparin is claimed to reduce catheter sepsis by preventing formation of a fibrin sleeve around the tip of the catheter[77], but this is debatable[78].

Gram staining of the catheter removed[79] and semiquantitative or quantitative bacterial cultures of the catheter tip[80] are being recommended for more accurate diagnosis of catheter sepsis. *Table 4* gives the diagnostic distinction between catheter sepsis and catheter infection and its management. The key to prevention is a rigid protocol for catheter maintenance and dressings and keeping line violation for administration of drugs, blood, and blood products to a minimum[81–83].

Cyclic TPN

If the patient is stable on TPN and not insulin dependent, TPN

Table 3 *Complications of catheter insertion incurred by a nutritional support team and a group of other physicians*

Complication	Complication rate (%) Team	Complication rate (%) Non-team
Pneumothorax	0	12
Haemothorax	0	2·3
Pleural effusion	0	0·76
Brachial plexus injury	0	0·76
Subclavian artery injury	0	1·8
Catheter embolism	0	1·28
Air embolism	0	0
Thoracic duct injury	0	0
Hydromediastinum	0	0·5
Catheter malposition	3·2	13·2
Total complications	3·2	33

Modified from reference 70: *J Am Med Assoc* 1980; **243**: 1906–8, © 1980 American Medical Association, with permission

Table 4 *Management of catheter infection and sepsis*

*PBC	†CBC	‡CTC	Diagnosis	Treatment
−ve	−ve	−ve	No sepsis	Nil
+ve	+ve	−ve	Sepsis probably not related to catheter	Change catheter over guidewire once a week
+ve	−ve	−ve		
−ve	−ve	+ve	Catheter infection	Change catheter over a guidewire
−ve	+ve	−ve		
−ve	+ve	+ve		
+ve	+ve	+ve	Catheter sepsis	Remove catheter and change to a new site
+ve	−ve	+ve		

Compiled from References 74, 80 and 82

*Peripheral blood culture; †blood culture drawn through the central line; ‡catheter tip culture

Additional rules:

1. All catheter sites should be inspected at least twice a week and dressing changed aseptically
2. If patient is septicaemic and catheter is not the source, change catheter over guidewire once a week to prevent seeding of the catheter tip
3. In case of *Staphylococcus aureus* sepsis or fungal septicaemia due to any source, change catheter to a new site
4. Change catheter to a new site if there is catheter exit-site infection

can be cycled in such a way that the patient has a glucose-free period for 10–12 h a day. This technique, known as cyclic hyperalimentation, decreases the duration of hyperinsulinaemia and hepatic lipogenesis and improves hepatic function[84,85]. In some cases, it allows the patient to be more mobile and is the usual mode of administration in patients on home TPN.

Pre-operative TPN

Several controlled studies have attempted to establish whether adequate pre-operative nutritional repletion reduces the postoperative complication rate[86–89]. These studies indicate that, if TPN is administered for 7–10 days pre-operatively, an advantage may be seen in terms of a decreased rate of postoperative wound infections[88,89], improved wound healing and weight gain[86], as well as an improvement in the rate of major postoperative complications and mortality[87]. Each of these studies has been criticized because of small patient numbers. However, when considered in aggregate, the patients given pre-operative TPN had a statistically significant advantage in terms of improved morbidity. Studies which have failed to demonstrate benefits from pre-operative TPN can be criticized, in that hyperalimentation was given for too short a period or to patients whose nutritional status (pre-operative albumin greater than or equal to $34\ \mathrm{g\ l^{-1}}$) placed them at low-risk of postoperative complications.

We usually give pre-operative nutritional support for at least 7 days in patients: (1) whose serum albumin on admission is $<30\ \mathrm{g\ l^{-1}}$, (2) who have experienced a recent unintentional weight loss of $\geqslant 10$ per cent of usual body weight, and/or (3) who demonstrate skin test anergy (in the absence of steroid administration). Generally, studies which have established an advantage for pre-operative TPN have given 30–45 $\mathrm{kcal\ kg^{-1}\ day^{-1}}$ and 1·2–1·5 $\mathrm{g\ protein\ kg^{-1}\ day^{-1}}$. A mixed fuel system is preferred. However, a mixed fuel system may not be effective if lipid is administered in cyclic fashion or in large quantities. Muller and associates, in a recent clarification of their original study, found a mixed fuel system to be ineffective and attributed this to excess lipid blocking the reticulo-endothelial system[90]. It should be emphasized that, if gastrointestinal function is intact, enteral nutritional repletion has been shown to result in the same benefits in terms of reduced postoperative complications[91].

TPN in different disease states

The metabolic disturbances and the pathogeneses of different surgical disorders vary so much that the administration of TPN is considered for individual surgical conditions.

TPN in inflammatory bowel disease

Decreased dietary intake, malabsorption, protein-losing enteropathy and multiple abdominal operation often lead to a state of chronic malnutrition. Diarrhoea results in excessive loss of cations such as Na^+, K^+, Mg^{2+} and Zn^{2+} as well as dehydration. Therefore, an adequate supply of fluid, electrolytes and trace minerals, in addition to protein and energy, is vital in order to preserve body cell mass and the host defence mechanisms[92]. Barot and associates found that the inflammatory bowel disease patients with weight losses of greater than 10 per cent of their ideal body weight had higher energy expenditure than would be estimated using the Harris–Benedict formula[29]. This difference between measured and calculated energy expenditure is attributed to elevated disease activity. They also suggest that, in the absence of significant weight loss or sepsis; these patients are not hypermetabolic[29]. In situations where multiple stress factors are combined, indirect calorimetry may be invaluable[92].

Typically, TPN is used pre-operatively, in patients who develop postoperative complications, or in patients who undergo massive intestinal resection and have permanent gut failure. Some studies of pre-operative TPN in inflammatory bowel disease suggest a decreased incidence of postoperative complications and increased rate of bowel resections[93], while one study suggested a slight increase in hospital stay and incidence of complications[94]. One survey revealed that patients who need urgent surgery are more malnourished and more likely to need nutritional support[95].

TPN can be regarded as primary therapy for inflammatory bowel disease when it is indicated after failure of the standard medical treatment, but surgery is not performed[92]. However, the quality of evidence for the benefit of TPN in inflammatory bowel disease is poor[96]. There has been no controlled study using TPN as the only primary mode of therapy[97–100]. A recent study showed a 60 per cent remission rate in the nonfistulous group and a 36 per cent rate in the fistulous group at the end of one year[101]. If these results are compared with the remission rate achieved with other conventional strategies, TPN in conjunction with complete bowel rest appears to be an effective form of therapy.

There are two main differences between ulcerative colitis and Crohn's disease that must be considered in any analysis of the effects of TPN on disease activity. In ulcerative colitis, disease is restricted to the colon and patients will be completely cured by total colectomy. On the other hand, Crohn's disease patients with small bowel involvement will have more nutritional deficits and may have a more favourable response to bowel rest and nutritional repletion[92]. Furthermore, the clinical course of fulminant colitis is unlikely to be altered by TPN. Therefore, in most studies, the clinical course of patients with ulcerative colitis does not appear to be significantly influenced by TPN[97,100]. Patients with inflammatory bowel disease are more prone to mechanical, septic and metabolic complications of TPN, particularly because they may receive multiple courses of TPN over extended periods[92]. These patients also tend to develop antithrombin-III deficiency and may be more prone to subclavian vein thrombosis[73].

TPN in enteric fistulae and short gut syndrome

The most significant impact of TPN on survival rates is in this group of patients. For instance, 30 years ago mortality rates for gastroduodenal, small bowel and colonic fistulae were 62 per cent, 54 per cent, and 16 per cent[102] as opposed to the current rates of 30 per cent, 25 per cent and 14 per cent respectively[103]. The important principles of management of an enteric fistula are control of drainage and protection of the skin, control of infection, definition of anatomy, nutritional evaluation and therapy and operation, if necessary[104]. The lowest mortality rate associated with gastrointestinal fistulae was demonstrated by Dudrick when he documented a spontaneous closure rate of 70 per cent and a mortality rate of 6 per cent in a series of 78 patients[105]. Fistulae in the upper part of the gastrointestinal tract with large output more often need TPN, while fistulae in the lower part of the small bowel and colon can be managed by enteral formulae[104]. Traumatic fistulae have a high tendency for spontaneous closure with TPN, but the results are poor when there is distal obstruction or underlying organic pathology such as inflammatory bowel disease, cancer or radiation enteritis[104]. Nevertheless, in complex enteric fistulae not amenable to any other form of therapy, home TPN prevents the patients from being nutritional cripples. At present, the common cause of death in patients with enteric fistulae is uncontrolled sepsis.

After massive resection of bowel, particularly if only 60–80 cm of small bowel is left, the patient invariably needs long-term TPN[106]. In the initial stages, substantial quantities of fluid (6–8 l day^{-1}), sodium (300–400 mmol), potassium (100–200 mmol) and other electrolytes and trace minerals may have to be supplied. Great potential variation in day-to-day requirements calls for close monitoring. Gradually, as the remaining bowel adapts, there is better tolerance of oral fluids and stabilization of the TPN regimen, facilitating the patient's discharge to home TPN[105].

TPN in acute and chronic pancreatitis

It is apparent that patients with severe pancreatitis and its complications may need TPN to maintain adequate nutritional status. However, there is no prospective, randomized, controlled study to prove the value of TPN as the primary therapy in these cases[107]. Also, it is unclear from experimental animal data to what degree pancreatic secretions are altered by parenteral as opposed to enteral nutrition. The administration of intravenous nutrients in dogs stimulates pancreatic secretion[108], but to a lesser degree than enteral feeding[109]. Others have been unable to demonstrate any differences in pancreatic secretion in dogs when intravenous and enteral feeding were compared[110]. One interesting study demonstrated a reduction in pancreatic mass in parenterally fed dogs associated with decreased serum gastrin levels[111]. These authors suggest that gastrin, secreted in increased amounts during enteral feeding, may have a trophic effect on the pancreas and, thus, contribute to increased pancreatic secretion.

Clinical trials have demonstrated the usefulness of TPN in promoting the spontaneous closure of pancreatic fistulae, suggesting that pancreatic secretion is effectively reduced[112]. In patients with severe acute pancreatitis, aggressive intravenous nutritional support decreased the complication rate when compared with historic controls[113]. Others have highlighted the importance of maintaining adequate nutritional support[114] to optimize the stress response in the acute stage of the disease. Repletion of nutritional defects secondary to pain-associated anorexia and malabsorption may also be needed in chronic pancreatitis.

Due to the association of hyperlipidaemia with acute pancreatitis[115,116], there has been some concern about the administration of lipid emulsion to patients with this disorder. Intravenous lipid administration stimulates pancreatic secretion in dogs[108]. However, studies in healthy volunteers and patients with acute pancreatitis have shown no increase in pancreatic secretion[116], nor any exacerbation of symptoms[117]. At present, it would seem prudent not to administer lipid emulsions to patients with pancreatitis who have a prior history of lipid-related metabolic disorders.

In terms of overall survival in acute pancreatitis, some authors have shown improvement with TPN[118], whereas others have not[119], and the issue remains unresolved.

TPN in cancer

Malnutrition and cachexia are common in cancer patients. The degree of catabolism depends on the type and extent of the tumour[120]. Moreover, if anorexia and decreased intake were the only cause of cancer cachexia, TPN would completely eradicate malnutrition[121]. Studies of patients with oesophageal and gastric neoplasia have shown a decrease in surgical complications in patients receiving TPN perioperatively[86,88]. As far as chemotherapy and radiotherapy are concerned, TPN may be recommended only until the patient recovers from the side effects of therapy. TPN itself will not influence the responsiveness of the tumour or the ultimate outcome of therapy[121,122], at least from the results of randomized clinical trials. At present, it seems unwise to pursue aggressive nutritional support in a patient who has advanced malignancy with no possible cure. Although studies have documented increased rates of tumour growth in animals receiving exogenous nutrition[120,123], most of these involve transplanted tumours of large bulk so that their sensitivity to nutrient supply may be very different from that of spontaneous human tumours[123]. Brennan suggested that the cancer cachexia patients differ markedly from those with simple starvation in that they have lost their adaptive mechanisms needed for body conservation[124]. The results of protein-kinetic studies in these patients parallel those found in stressed patients, with high protein turnover and net skeletal muscle loss. In the light of these findings, recent studies employing branched chain amino acid enriched solutions have demonstrated improved protein kinetics and increased albumin synthesis[125]. The complexity of cancer cachexia warrants treatment on an individual basis. The goal is to arrest weight loss, support host defence mechanisms, and improve the quality of life[126].

TPN in the critically ill

Increased metabolic stress, multiorgan failure and sepsis lead to the rapid development of protein-calorie malnutrition[127], whereas fluid overload, increased water retention due to high aldosterone and antidiuretic hormone activity limit the volume of fluid that can be administered[30]. In the initial stages, the aim is to limit catabolism and to provide protein and calories to maintain the host defence mechanisms[128], respiratory muscle strength, and the integrity of the pulmonary parenchyma[129]. Anabolism and positive nitrogen balance ensue as the patient recovers. Overfeeding with glucose results in excessive carbon dioxide production due to increased lipogenesis and may lead to difficulty in weaning from the ventilator[128]. In septic states there is modulation of the action of pyruvate dehydrogenase leading to blockade of the entry of pyruvate into the citric acid cycle, resulting in decreased oxidation of glucose and insulin resistance[129]. In a randomized trial, Baker and associates demonstrated that critically ill patients are not severely hypermetabolic and they can maintain protein balance with a modest excess of calories while using a wide range of fuel mixtures[130].

As protein catabolism is an integral part of prolonged sepsis, the anticatabolic properties of branched chain amino acids and their ability to improve hepatic protein synthesis might have been expected to have a significant impact on the survival of septic patients. Nevertheless, studies in critically ill patients have documented marginal improvements in nitrogen balance and improved visceral protein synthesis, but no effect on the overall survival rate[131]. Lipid emulsions are useful in limiting the volume and reducing the risk of excess carbon dioxide production. Triple lumen catheters increase the risk of sepsis when compared with single lumen catheters[132] but are useful in providing multiple access for TPN, haemodynamic monitoring and administration of drugs. In critically ill patients, a typical TPN prescription includes 1000–1500 ml volume, 6 per cent amino acids, 15 per cent dextrose and 3 per cent lipid.

Hepatic encephalopathy

A number of metabolic alterations observed in patients with hepatic encephalopathy have given room for various hypotheses. Two predominant hypotheses have generated particular experimental data and interest.

Synergism hypothesis

In the presence of hepatic failure, encephalopathy and ultimately coma result from synergistic effects of accumulating toxins. Ammonia, mercaptans and fatty acids are the commonly identified toxins. The toxins interact synergistically to produce neurological alterations which are out of proportion to the resulting abnormality when they are administered singly. Accumulation of ammonia and its effects on the central nervous system are central in the synergism hypothesis[133].

False neurotransmitter hypothesis

The amino acid pattern is altered in liver disease with decreased quantities of branched chain amino acids relative to aromatic amino acids. This leads to increased entry of aromatic amino acids into the brain with synthesis of false neurotransmitters such as octopamine and decreased synthesis of dopamine and noradrenaline. Fischer and associates formulated this hypothesis in 1971, and ammonia was not considered to be a primary factor in the pathogenesis of encephalopathy[134]. The same group developed a unified hypothesis in 1979, noting that patients with encephalopathy have elevated levels of glutamine in the cerebrospinal fluid. According to them, ammonia entering the brain is rapidly combined with glutamate to form glutamine, and the brain, in its efforts to normalize neutral amino acid levels, rapidly exports glutamine by the same mechanism responsible for the influx of neutral amino acids. Thus, ammonia indirectly contributes to encephalpathy by increasing amino acid imbalance in the brain[135]. Animal experiments do indicate a relationship between octopamine and coma, but changes in brain dopamine and noradrenaline have never been shown to cause coma[133]. Thus, although there is plasma amino acid imbalance in encephalopathy, it is uncertain whether the relationship is causal.

Fischer demonstrated initially that administration of branched amino acid enriched solution to patients with encephalopathy corrects the amino acid pattern with improvement in the encephalopathy[136]. Since then, there have been many branched chain amino acid trials and the results have been conflicting. It is difficult to interpret the results of these trials as they are designed very differently. However, some conclusions can be drawn regarding protein supply in encephalopathy:

1. Branched chain amino acids are safe when given orally[137] and parenterally[136].
2. Oral branched chain amino acids[137], casein modular diet[138] and vegetable protein[139] seem to be better tolerated than dietary meat protein.
3. Branched chain amino acids can induce positive nitrogen balance, but it is essential to supply at least 75 g of protein for an adequate length of time[131].
4. A number of trials which have used branched chain amino acids and hypertonic dextrose have documented improvement in hepatic encephalopathy[140,141], and one recent study has also demonstrated slight improvement in the mortality[141].
5. There have been no trials comparing branched chain amino acids and standard amino acid solutions in hepatic encephalopathy.

Branched chain amino acids improve hepatic protein synthesis and reverse the catabolic state characteristic of cirrhosis[142]. Although more confirmation is needed regarding the anticatabolic properties of branched chain amino acids, it seems wise to administer them when protein intake is restricted, at least for metabolic if not for neurological reasons.

The exact role of fat emulsions in liver disease is not defined. There is some evidence that fatty acids can displace the albumin bound tryptophan and, thus, theoretically increase the risk of encephalopathy[143], but it has also been demonstrated by indirect calorimetry that fat degradation in patients with liver disease is increased from 50 to 84 per cent of the normal value[144]. Fat appears to be an important substrate in severe liver disease[145].

Acute renal failure

The protein and energy requirement of these patients are the same as that of any other patient[128]. Therefore, if the patient is being dialysed, he should be provided with estimated amounts of calories and protein. One study demonstrated a reduced rate of blood urea nitrogen levels and improved survival from renal failure after treatment with small amounts of essential amino acids[146]. It was hypothesized that this was due to recycling of urea for the synthesis of non-essential amino acids. Nevertheless, it now appears that such re-utilization of urea is very limited[147]. If dietary protein has to be restricted for a brief period, it would be appropriate to supply protein rich in essential amino acids, to prevent nutritional deficiencies. However, for longer periods, it is advisable to initiate dialysis to allow the intake of at least 1 g/kg^{-1} body weight. As mentioned earlier, a case could also be made for the use of branched chain amino acids if there is protein restriction[41–43]. It is useful to remember that there can be considerable dextrose absorption and protein loss during peritoneal dialysis. Particular attention is paid to fluid, potassium, magnesium and phosphate needs in this group of patients.

Monitoring of the nutritional support

Accurate daily weight recordings are useful in assessing the patient's fluid status. Serum electrolyte measurements may be needed twice a week or more often, depending on the degree of electrolyte disturbance. Actual bicarbonate and arterial blood-gas values are needed to assess acid–base status and plan appropriate therapy, particularly in the critically ill.

Urinary electrolyte determinations assist in planning electrolyte replacement. Nitrogen balance studies carried out at least once a week with 24 h urine collections will help in dynamic assessment. The nitrogen balance is calculated as:

$$\text{nitrogen balance (g)} = \frac{\text{protein intake (g)}}{6{\cdot}25} - 24\text{ h urinary urea nitrogen (g)} + 4$$

One can anticipate 4–6 g positive nitrogen balance each day, representing 25–37·5 g protein and 120–180 g of lean tissue, when a malnourished adult without significant stress receives[8] 40 kcal and 1·5 g protein (kg body weight)$^{-1}$ day^{-1}.

Delayed hypersensitivity skin testing can be an early index of the return to normal following adequate nutritional repletion. Serum transferrin (half-life of 10 days) and serum albumin (half-life of 20 days) respond more slowly. If significant metabolic stress persists, the serum albumin level may not respond in spite of adequate nutritional support[8,16].

Nutritional support team

It is essential to provide a TPN service with minimal complications and a high degree of effectiveness[148]. Several studies have conclusively demonstrated that the service provided by an organized team has less mechanical, septic and metabolic complications[70,148–151]. It could be anticipated that this is more cost effective. The nutrition team needs a surgeon or physician with a knowledge of metabolism and experience in central-line placement, a nurse trained in catheter dressings, a pharmacist with a knowledge of physicochemical compatibilities of TPN solutions, and a dietician to offer assistance in the transition to enteral or oral feeding[148]. Apart from the quality of care, the team approach helps in better training of juniors and in conducting research, particularly controlled clinical trials. When formation of a team is not feasible, a surgeon or physician with a reliable catheter insertion technique, constantly aware of possible septic and metabolic complications, may initiate and maintain TPN, but in more complicated cases, expert help is available[70].

Cost effectiveness of parenteral nutritional support

Specialized nutritional support, especially intravenous support, is expensive. In every country, health-care rationing in some form is inevitable, since demand is potentially unlimited while resources are limited. It is important to demonstrate benefits of TPN to justify the risks and costs associated with the therapy. This, in turn, requires controlled clinical trials large enough to avoid type-II errors.

The lifesaving benefits of TPN in the short gut syndrome and high enteric fistulae are very clear. The areas that need to be studied extensively are the provision of TPN in advanced malignancy and the pre-operative use of TPN in attempts to reduce morbidity and mortality. The large Veterans Administration trial in progress in the USA may answer some of these questions definitively. A cost-benefit analysis of the results of the pre-operative TPN trials of Muller and Heatley demonstrated that considerable monetary benefits accrue if surgical complications are reduced by perioperative TPN[152]. To keep TPN cost effective, it should be used only when indicated (when enteral nutrition is not feasible), only in patients where a clear-cut benefit has been demonstrated, and when the complications associated with its administration can be kept at their lowest possible levels[152–153].

Acknowledgements

Conclusions drawn and therapeutic recommendations in this review reflect practice by the Nutritional Support Service at New England Deaconess Hospital, Harvard Medical School, which consults on more than 350 patients annually with an average of 6000 patient days on TPN each year.

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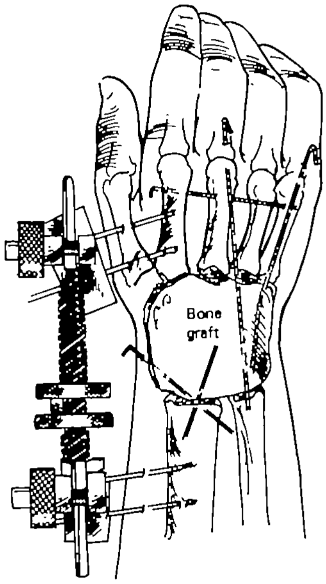

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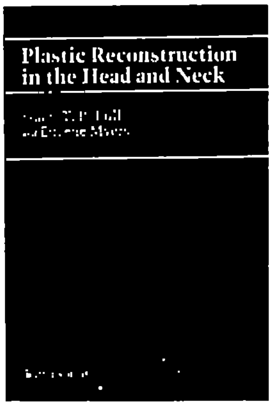

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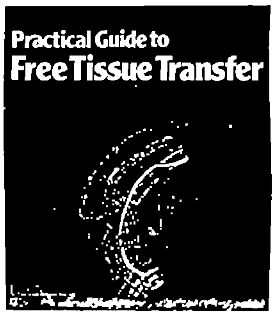

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Management of traumatic rupture of the diaphragm

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Traumatic rupture of the diaphragm is a potentially serious injury which presents in different forms depending on the mechanism of the causative trauma. Over a 7 year period, 20 patients (17 male and 3 female) with traumatic rupture of the diaphragm were seen in our unit; their mean age was 25·6 years. Automobile accidents caused the diaphragmatic injuries in 65 per cent of cases while falls from trees were the cause of injury in 10 per cent. Ten patients (50 per cent) were seen within 7 days of the injury and 95 per cent within 3 months. The left hemidiaphragm was ruptured in 85 per cent and the right in 15 per cent of cases. Fifty ribs were fractured in fourteen patients (70 per cent) but there were no pelvic fractures. Fourteen patients (70 per cent) had gastrointestinal visceral herniation into the thorax, the stomach, omentum, colon and spleen being the commonest herniating organs. Successful surgical repair was achieved in 18 patients, 4 of whom also had splenectomy; 2 patients were treated conservatively. A high index of suspicion and early surgical treatment are the mainstay of successful management of traumatic rupture of the diaphragm with or without herniation of abdominal organs.

Keywords: Abdominal injuries, traumatic diaphragmatic hernia, splenic rupture, rib fractures

Traumatic rupture of the diaphragm is an internal injury which is rarely lethal itself, but which, if ignored or undetected may produce serious complications associated with gastrointestinal herniation. Though the diaphragm can rupture spontaneously[1] and may be torn during surgical operations[2], most diaphragmatic ruptures are caused by indirect (crushing) or direct (penetrating) injuries to the chest, abdomen or both. The earliest description of herniation of the abdominal viscera through a traumatic rupture of the diaphragm is credited to Sennertus in 1541[3]. Pare in 1579[4] described the clinical manifestations of traumatic diaphragmatic hernia, and in 1853 Bowditch[5] made a clinical diagnosis of ruptured diaphragm and described the five clinical signs of traumatic diaphragmatic hernia that remain useful for diagnosis today. Several authors[6–8] in the early part of this century described isolated cases of traumatic rupture of the diaphragm. Larger series of traumatic diaphragmatic rupture have been reported in the later part of this century from different centres corresponding with increased mechanization and criminal violence[9–11]. We report our experience with traumatic diaphragmatic rupture and hernia in a developing country.

Patients and methods

The patients were referred to our unit (which provides over 95 per cent of cardiothoracic surgical services in our hospital) for thoracic or thoraco-abdominal injuries during the 7 year period October 1977 to September 1984. Diagnosis was suspected from clinical signs and symptoms, and confirmed by radiological investigation or at operation. After resuscitation, surgical exploration and repair were performed through a thoracotomy, or a thoraco-abdominal incision or a laparotomy. Anaesthetic management consisted of atropine pre-medication and the 'crash' induction and relaxation technique with thiopentone sodium, suxamethonium bromide (0·5 mg/kg), endotracheal intubation, intermittent positive pressure ventilation with nitrous oxide/high oxygen mixture, and IV pancuronium bromide (0·1 mg/kg). A nasogastric tube was placed before induction. IV pethidine (0·5 mg/kg) was administered intermittently to supplement analgesia.

Thoracotomy through the bed of the 8th rib (occasionally extended into the abdomen and sparing the costal cartilage) was the common approach. After separating pleural adhesions and evacuating any pleural fluid, the hernial contents were inspected and reduced; the diaphragmatic tear was identified and the edges mobilized, and approximated with interrupted 2/0 Mer silk or Ethiflex sutures (Ethicon Ltd, Edinburgh, UK). A releasing incision was performed in one case to facilitate adequate approximation. Occasional reinforcing mattress sutures were inserted, and the suture-line on the pleural surface then covered with another row of interrupted 3/0 Mer silk sutures. Splenectomy was performed for splenic lacerations, gastric, hepatic and lung lacerations were suture-repaired while the necrotic omental tear was excised and repaired.

Pleural and/or peritoneal lavage was performed with Ampiclox–saline solution, and an appropriate pleural or splenic-bed drain inserted. The incision was closed in layers and associated soft tissue or limb injuries treated as necessary. Rib fractures were treated conservatively[12]. The patient was nursed in the intensive care unit for at least 72 h.

Results

There were 20 patients aged between 10 and 34 years (mean 25·6 years); 17 were males and 3 were females. *Table 1* shows that automobile accidents were the causative factor in 13 patients; 2 patients fell from fruit trees. Most of the injuries were indirect or crushing.

Clinical and radiological features (Table 2)

One patient had previous thoraco-abdominal exploration for a penetrating perineo-abdominal injury and later presented with obstructive dysphagia due to gastro-oesophageal herniation. Another patient was explored at the referring hospital for suspected peritonitis after a kick in the abdomen. Symptoms had been present between 24 h and 12 months, but the majority (95 per cent) of the patients presented within 3 months of the injury. The left diaphragm was involved in 17 patients (85 per cent) and the right hemidiaphragm in 3 patients (15 per cent). In the 14 patients with rib fractures, there was a total of 50 fractured ribs: 37 on the left side, and 13 on the right.

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Table 1 *Mechanism of injury*

	Number	Percentage
Automobile accident	13	65
Fall from height	2	10
Falling object	1	5
Blast from a gun	1	5
Kick on the abdomen	1	5
Gunshot	1	5
Stab with knife	1	5
Total	20	100

Table 2 *Clinical and radiological features of diaphragmatic rupture*

	Number of patients	Percentage
Main symptoms		
Chest pain	13	65
Dyspnoea	12	60
Cough	6	30
Vomiting	6	30
Abdominal pain	5	25
Dysphagia	4	20
Main physical signs		
Diminished breath sounds	19	95
Dyspnoea	13	65
Shock	9	45
Abdominal tenderness	8	40
Haemorrhage/anaemia	7	35
Bowel sounds in the chest	6	30
Radiological findings		
Rib fractures	14	70
Elevated (or loss of) diaphragmatic outline	10	50
Gastrointestinal shadows in the thorax	10	50
Haemothorax/pneumothorax	7	35
Lung atelectasis	6	30

The majority of the fractures were of the 7th–10th ribs, but there was no fracture of the right 10th rib. A barium meal was performed in three patients to confirm intrathoracic gastrointestinal herniation. Associated thoracic and extrathoracic injuries are listed in *Table 3*; they reflect the severity of injuries in the patients.

Diagnosis

This was established clinically and radiologically in 18 cases and at operation in 2 patients: in a boy of 10 years who received a kick in the abdomen and was explored at the referring hospital and in a 25-year-old police officer who sustained a gun shot wound through the left 8th intercostal space posteriorly.

Treatment

This was conservative in two patients with fractured ribs, mild haemothoraces and elevations of the diaphragm but with no evidence of abdominal visceral herniation. The remaining 18 patients received operative treatment; 6 of them had emergency operations. The operative findings are summarized in *Table 4*. Most of the diaphragmatic ruptures involved the muscular and tendinous parts of the diaphragm, while the stomach and colon (often with the omentum) were the commonest organs to herniate. Splenectomy was performed in four patients for severe lacerations, but there was no indication for gastrointestinal resection. There was no operative mortality. Significant postoperative complications were basal lung atelectasis in two patients and moderate wound infection in three patients, all of whom responded to treatment before discharge. Those patients treated conservatively have not developed significant symptoms during a follow-up period of 12 and 30 months respectively; their diaphragmatic elevations have diminished.

Discussion

Since the first descriptions of traumatic rupture of the diaphragm with abdominal visceral herniation[3,4], several reports[5–11] have underlined increasing incidence due to major trauma from automobile accidents, and the problems of diagnosis and management. Automobile accidents accounted for 65 per cent of our cases and 92–100 per cent in other series[9–11]; however, the 4·1 per cent incidence of ruptured diaphragm in our patients with chest trauma[12] is similar to the incidence in the larger series of Alyono and Perry[13].

Our oldest patient was 34 years, thus reflecting the preponderance of the younger age group in our population in contrast to industrialized countries where much older patients were also injured[14]. A serious complication of diaphragmatic rupture is the early or late intrathoracic herniation of the abdominal viscera[10,15–17]. Based on the three stages of presentation (acute, latent or chronic and late[15]), 50 per cent of our patients presented in the acute stage with dyspnoea and shock from intrathoracic or intra-abdominal haemorrhage or pneumothorax. Only one patient presented late (after 1 year) with gastrointestinal obstruction. The remaining patients presented in the latent or chronic stage because of respiratory embarrassment, chest pain, gastrointestinal discomfort and dysphagia.

Traumatic diaphragmatic hernia is often missed because of the presence of associated injuries[11], minimal initial symptoms or the difficulty in differentiating other radiological conditions (lung atelectasis, tension pneumothorax, and pleural effusion) which may be associated with a ruptured diaphragm. Ruptured right hemidiaphragm is difficult to diagnose since the herniated liver may be mistaken for an elevated intact diaphragm[14]. Diagnosis is based on a high index of suspicion especially in a patient with a history of direct or indirect trauma to the trunk[11]. If this suspicion is overlooked, the problems of such serious complications as delayed gastrointestinal herniation,

Table 3 *Associated injuries in rupture of the diaphragm*

	Number of patients	Percentage
Thoracic		
Rib fractures	14	70
Pleural tear	7	35
Lung laceration	2	10
Pericardial rupture	1	5
Abdominal		
Splenic laceration	4	20
Gastric laceration	3	15
Hepatic laceration	2	10
Omental tear	1	5
Wall (lumbar hernia)	1	5
Others		
Limb fractures	2	10
Soft tissue (hand and face)	2	10
Perineal	1	5

Table 4 *Operative findings in 18 cases of diaphragmatic rupture*

	Number of patients	Percentage
Site of rupture		
Muscular and tendinous parts	9	50
Muscular part only	7	39
Tendinous part only	2	11
Herniating organ		
Stomach	9	50
Omentum	9	50
Colon	6	33
Spleen	5	28
Liver	3	17
Small intestine	2	11
Others		
Pericardial rupture	1	6

obstruction and perforation may result. Diganosis can be confirmed by radiological screening of the diaphragm, passage of a nasogastric tube, a barium meal or enema and by real-time sonography[18]. Correct pre-operative diagnosis has been achieved in about 70–85 per cent of cases[10,19]; we achieved 90 per cent pre-operative diagnosis, though this was possible in only a third within the first 48 h.

In our patients and in those of Sutton and colleagues[19], the left hemidiaphragm was ruptured about six times more often than the right but higher ratios of 14:1 and 20:1 were reported by others[11,20]; the splinting and cushioning effect of the liver protects the right hemidiaphragm from rupture in indirect trauma. The commonest sites of rupture in this and other studies were the central and posteriocentral tendinomuscular parts which correlate with the embryologic areas of weakness of the diaphragm[1,21]. Ruptures of the anteriolateral and paracardiac parts may extend into the pericardial cavity and cause cardiac compression by the herniating viscera[22]. A combination of mechanisms including transmission of forces through abdominal viscera[16,23], distortion of the tightly stretched diaphragm[24] and respiratory efforts[25] may cause the rupture at any given occasion.

The absence of pelvic injuries and the rarity of significant head injuries in our patients contrast with the high incidence reported by others[10,11,26–28], and may be due to the type and speed of the automobiles associated with the injuries.

Prevention of the complications of gastrointestinal herniations and the presence of signs of cardiorespiratory embarrassment are indications for surgical repair of the rupture[14]. We and others[11,14,29,30] preferred the thoracic approach, especially in the early stage of left-sided rupture, and in the late or chronic stage when intrathoracic adhesions have developed. A thoraco-abdominal approach may be necessary when upper abdominal viscera are also injured. The anaesthetic management of patients with diaphragmatic hernia is an important aspect of the surgical treatment. In addition to the pre-operative stabilization of associated shock and electrolyte disturbances, the contents of the dilated bowel should be aspirated before and during operative procedures to prevent regurgitation and aspiration of gastrointestinal contents into the lungs. The anaesthetic problems of traumatic diaphragmatic hernia have been highlighted by Loehning and colleagues[31], who also reported cardiac arrest or severe hypotension during anaesthetic induction, and made recommendations for preventing circulatory collapse. Our anaesthetic technique, which included their 'crash' induction technique, was not associated with significant circulatory collapse.

The morbidity and mortality of ruptured diaphragm depend largely on early or late presentation and diagnosis, the degree of rupture, associated chest or head injuries and careful postoperative management. Successful repair in all our patients was due to 'early' recognition, and the absence of severe head injuries or complicating intestinal strangulation or perforation.

Acknowledgements

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Indium-111-labelled leucocytes in the diagnosis of abdominal abscess

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The extensive morbidity and mortality of intra-abdominal abscess is mainly due to the delay in a diagnosis. The diagnostic accuracy of ^{111}In-labelled mixed leucocytes with gamma imaging has been investigated in 100 consecutive patients including 34 following surgery and 36 with inflammatory bowel disease. White cell scans were performed 24 h following injection of autologous ^{111}In-labelled leucocytes and were compared with clinical outcome where abscess was only diagnosed when pus either discharged or was drained at operation. Gamma images detected 28 of the 30 abscesses with no false positives giving 93 per cent sensitivity and 100 per cent specificity. Loculi of pus were identified in 11 of the 36 patients with inflammatory bowel disease with no errors in interpretation. Inflammation was reported in 15 of the remaining 25 patients with known but not necessarily active inflammatory bowel disease. ^{111}In-labelled leucocyte imaging provides a rapid, safe and precise method for detecting intra-abdominal abscess even in the presence of inflammatory bowel disease.

Keywords: Abscess diagnosis, radiolabelled leucocytes, inflammatory bowel disease

The overall mortality of intra-abdominal abscess remains high at approximately 30 per cent[1,2]. In survivors the morbidity is severe with hospital treatment for the more difficult to diagnose visceral or retroperitoneal abscesses extending to a mean of more than 10 weeks. The most important cause for this extensive morbidity and mortality is reported to be the delay in diagnosing and localizing sepsis[1,2], because the traditional clinical signs may be absent and usually fail to indicate the site of infection. Where an abscess is suspected the anatomical abnormality is best displayed by ultrasound or CT scanning with which abnormal fluid collections will be located in over 90 per cent of patients[3]. Unfortunately neither of these investigations can be relied upon to distinguish collections of serous fluid or haematoma from pus[4]. Furthermore, the pus and gas within an abscess may easily be confused with the intestinal contents which limits the value of X-ray and ultrasound techniques in patients with inflammatory bowel disease.

The use of radiolabelled leucocytes represents a 'functional' approach to detecting pus, whether in an abscess or in other sites. Initially, this was achieved by the use of [^{67}Ga] gallium citrate but 15 per cent of this isotope is excreted into the bowel obscuring the abdominal scan[5]. In practice, where cell labelling facilities exist, ^{67}Ga has been superceded by ^{111}In-labelled leucocytes and we investigated the sensitivity and specificity of this latter technique in 100 consecutive patients.

Methods

Patients

Of the 100 patients aged 15–80 years with sepsis suspected clinically, 34 were postoperative and 36 had inflammatory bowel disease (*Table 1*). Assessment was prospective with the clinical details on all patients recorded on entry to the study. The final diagnosis was made after adequate out-patient review following hospital discharge. Abscess was diagnosed only where pus was seen to drain either spontaneously, at operation or on aspiration.

^{111}In-labelled mixed leucocyte label

The labelling technique used in this study was a modification of that originally described by Thakur *et al.* permitting a high labelling efficiency using only 17 ml of venous blood[6]. This was taken into 3 ml of acid citrate solution, mixed gently and allowed to sediment for 50 min at ambient temperature. The supernatant leucocyte and platelet rich plasma was then diluted using 20 per cent modified Tyrode buffer and centrifuged at 640*g* for 10 min[7]. The platelet rich plasma was removed and the residual leucocyte pellet resuspended in Tyrode buffer and incubated with 150 μCi of ^{111}In-labelled oxine (Amersham International) for 2 min at room temperature. Plasma was then added to quench the reaction and the labelled mixed leucocytes obtained by repeat centrifugation and resuspension in 5 ml and Tyrode buffer for intravenous administration.

Gamma scans

In all patients the abdomen and thorax were imaged over a 10 min period 24 h following labelling using a Searle LFOV gamma camera fitted with a medium energy parallel collimator and set to detect both ^{111}In photopeaks. A DEC PDP 11 computer was used for subsequent storage and manipulation of scans. Additional earlier scans at 4 h were taken in patients with inflammatory bowel disease. Where upper abdominal sepsis was suspected, liver and spleen subtraction using ^{99m}Tc colloid was performed by the standard techniques. All scans were reported by an independent clinician with experience in reading leucocyte studies and access to information on the clinical request form only. Abscess was diagnosed when abnormal radiolabelled cell accumulation was circumscribed and of comparable or greater activity to that over the liver[3] (*Figure 1*). Diffuse low grade uptake, especially in

Table 1 *One hundred patients investigated for abdominal sepsis*

Postoperative		34
Colonic surgery	12	
Appendicectomy	6	
Gastric and biliary	7	
Vascular	3	
Urological	3	
Miscellaneous	3	
Inflammatory bowel disease		36
Crohn's disease	33	
Ulcerative colitis	3	
Pyrexia of unknown origin		13
Miscellaneous abdominal and pelvic		17
Total		100

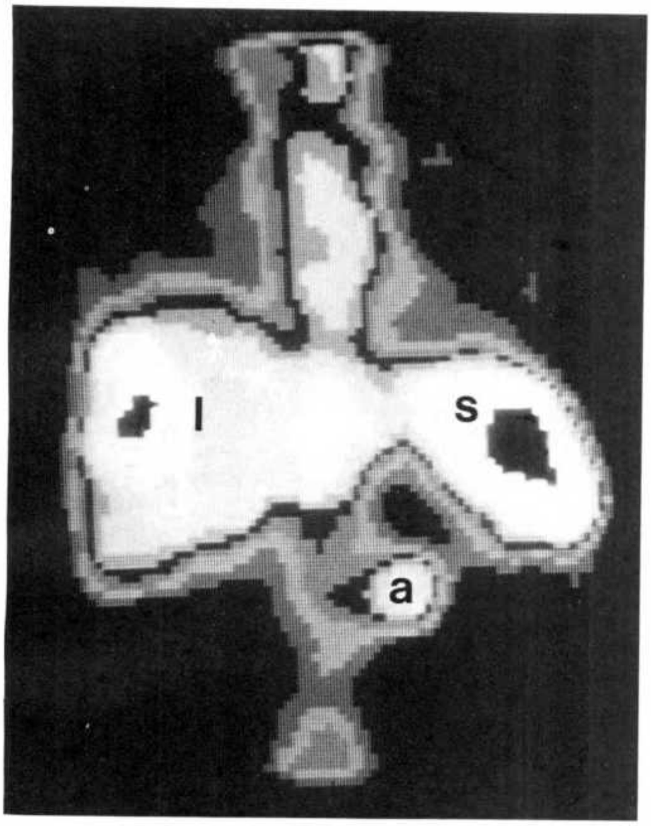

Figure 1 *This leucocyte scan is of the upper abdomen in a 62-year-old man 4 months following gastrectomy. Abdominal sepsis could not be localized despite four ultrasound studies and CT examination on two occasions. An abscess in the lesser sac is seen (a) with radioactivity equivalent to that over the liver (l) and even approaching that of the spleen (s)*

the bowel at 4 h, was considered to represent inflammation only. In every case the leucocyte scan was requested for its diagnostic value and no studies were undertaken following drainage or aspiration of pus.

Results

Abscess was confirmed by drainage of pus in 30 patients. In 28 of these, the abscess was reported in ^{111}In-labelled leucocyte scans. The two false negative reports were both in patients with pyonephrosis where liver and spleen subtraction had not been performed and where the activity in these organs may have obscured renal uptake. In the remaining 70 patients the leucocyte scans were reported as showing no abscess although inflammation was sufficiently intense to produce bowel uptake in 17 of the 36 patients with inflammatory bowel disease (*Table 2*). As has previously been reported in patients with Crohn's disease, the diseased segment was usually radioactive at 4 h but on subsequent imaging at 24 h the activity was usually found to have moved on to the distal bowel[8]. The two false negative and no false positive reports combine to give a sensitivity of 93 per cent, a specificity of 100 per cent and an overall accuracy in abscess diagnosis of 98 per cent.

Discussion

In this series, intense and localized ^{111}In-labelled leucocyte accumulation was invariably followed by confirmation of pus and is therefore a strong indication for aspiration or drainage. Greatest activity is seen in recent and relatively active acute abscesses but mature abscesses up to 18 months old were seen clearly. The failure to detect two pyonephroses is worrying and we believe explained by our earlier practice of scanning the anterior abdomen without liver and spleen subtraction. We now advise routine posterior and lateral views with subtraction wherever upper abdominal sepsis is suspected. We also recognize a reliable progression of leucocytes into the pus of an abscess: early gamma images, between 1 and 4 h after the injection of radiolabelled leucocytes, demonstrate rapid accumulation of radioactivity in sites of inflammation whereas at 24 h the radioactivity has moved into the pus with a reduction in activity over inflammation. Once this sequence was recognized, 4 and 24 h studies were performed which may have improved diagnostic accuracy compared to 90 per cent achieved with single scans at varying intervals following leucocyte labelling[9]. Where doubt still remains further scans at 48 h may resolve the issue. With increasing experience the often complex inflammation of inflammatory bowel disease could be reliably distinguished from collections of pus and in this series abscess was correctly detected or excluded in all 36 such patients (*Figure 2*).

Despite their precision, radiolabelled leucocyte techniques should not replace the use of ultrasound and CT scanning. Both are non-invasive and give immediate, reliable information on the presence of abnormal fluid collections. It is essential to use one or other technique with ^{111}In-labelled leucocyte studies to detect fluid overlying the liver and spleen, especially as it is in these organs that high background radioactivity may obscure abscess uptake. As most of our patients had a previous

Table 2 *The result of leucocyte scans compared with clinical outcome in 100 patients*

	Clinical outcome		
	Abscess	Inflammation	Normal
Leucocyte scan			
Abscess	28	—	—
Inflammation	—	17	—
Normal	2	26	27
Total	30	43	27

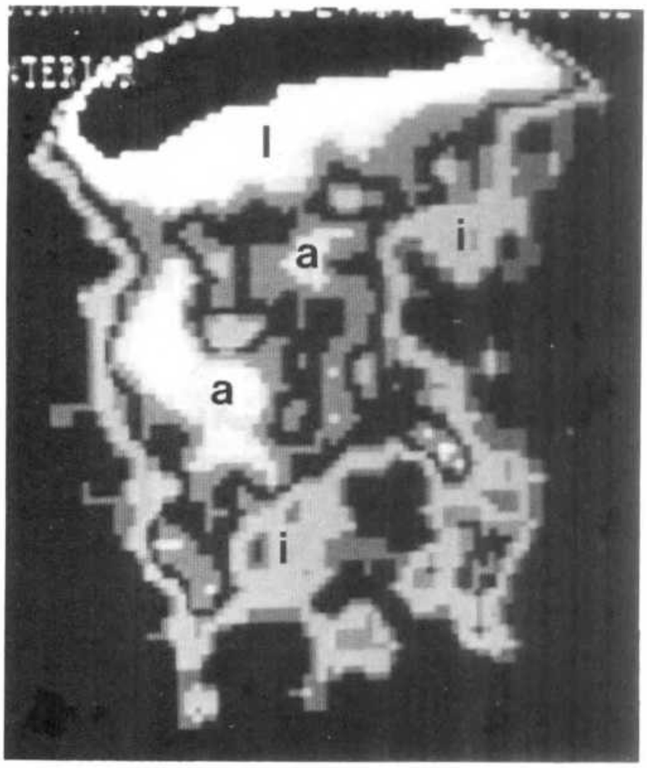

Figure 2 *The picture in patients with Crohn's disease may appear complex. The diagnosis of multiple abscess in the gamma image at 24 h could be confirmed as the activity in the abscesses (a) increased with time as leucocytes accumulate in the pus. The generalized activity associated with inflammation (i) is usually greatest at 4 h and moves along the bowel on subsequent images*

ultrasound or CT, their accuracy cannot be compared directly with leucocyte scans which in this study were specifically requested because of the failure of standard investigations to reach a diagnosis. Furthermore, both ultrasound and CT may be used to guide aspiration or catheter drainage both for diagnostic purposes and for definitive treatment[10,11]. Where percutaneous drainage is planned, a ^{111}In-labelled leucocyte study provides insufficient definition to guide needle puncture but may usefully exclude other sites of intra-abdominal sepsis reducing the need for full laparotomy.

In this series six patients underwent repeated intensive investigation, including CT, ultrasound and exploratory laparotomy in two, which had failed to localize sepsis. Although the abscess was localized in all cases by ^{111}In-labelled leucocytes these patients had deteriorated to a critical condition, emphasizing the need for early referral to centres where cell labelling can be performed. ^{111}In-labelled leucocyte techniques are not difficult and could be used in most nuclear medicine departments. A 'clean room' is required both for sterility in an open cell labelling technique and for the stringent specifications of the Health and Safety at Work Acts. However, most hospitals do not have either the expensive facilities or staff trained in these methods and research should be directed to the development of an isotope substrate which either localizes directly in abscesses or may label leucocytes *in vivo*. In this way ^{111}In-labelled leucocyte techniques may be available early in the investigation of occult sepsis in any hospital possessing a gamma camera. Until then referral to those centres with the necessary facilities must be rapid to reduce mortality.

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Case report

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Recurrent small bowel obstruction associated with piroxicam

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It is known that small bowel ulceration and obstruction can be caused by drugs[1–4]. This report is of a patient who presented with recurrent small intestinal obstruction over 18 months while receiving piroxicam (Feldene) for arthritis.

Case report

A 75-year-old woman was admitted with an 18 month history of weight loss, abdominal pain and vomiting. She had been receiving piroxicam and Moduretic for 2 years. She had been admitted 6 months earlier with subacute small bowel obstruction. At that time she was anaemic (haemoglobin 8·1 g/dl, hypochromic microcytic type) and a small bowel series showed dilated small bowel, prolonged transit time and a suggestion of narrowing of the terminal ileum. At laparotomy thorough examination of the bowel revealed only a fibrosed appendix which was removed. After transient improvement her symptoms gradually recurred and worsened. Extensive investigations did not identify the cause. Her abdominal films on readmission suggested small bowel dilatation. On re-exploration an obstruction was identified some seventy centimetres proximal to the ileocaecal junction. Fifteen centimetres of the ileum, containing two diaphragm like strictures close together, was removed and intestinal continuity established with an end-to-end anastomosis. Following this, the patient experienced complete relief of symptoms.

Histology of the resected specimen revealed an area of ulceration with marked mucosal hypertrophy on both sides with chronic inflammatory cell infiltration and oedema of the submucosa. No malignant change was seen.

Discussion

Small bowel ulcers due to the use of certain drugs can lead to perforation, haemorrhage or obstruction with an overall mortality of up to 10 per cent[1,2]. A review[3] shows that drugs can cause small bowel obstruction by an effect on the mucosa (e.g. potassium supplements); by producing an intramural haematoma (e.g. anticoagulants); by affecting the smooth muscle (e.g. opiates); by interfering with parasympathetic nerve transmission (e.g. tricyclic antidepressants); or by an effect outside the wall (e.g. contraceptive pills and adrenal corticosteroids which may produce mesenteric vascular occlusion). Among the anti-inflammatory drugs, phenylbutazone has been implicated as a cause of small bowel obstruction due to multiple strictures[4].

This report emphasizes the need for caution in prolonged use of piroxicam in patients with gastrointestinal symptoms.

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Absorptive and motor function of orthotopically vascularized segmental ileal autografts

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In 24 dogs a 100 cm length of terminal ileum was autografted as an orthotopically vascularized Thiry–Vella segment. In six dogs absorption, motility and histology were studied in detail and in two intestinal myo-electrical activity was recorded. At a second operation 5 weeks after autotransplantation the Thiry–Vella segment was returned to its normal anatomical position in the intestinal stream and 2 months later all the non-transplanted intestine was resected. Eighteen grafts were technically successful. Intestinal myo-electrical activity was normal by the second day after transplantation while intestinal transit and contractile activity recovered within 10 days. Mucosal morphology and intestinal absorption had largely recovered by 10 days after grafting but absorption of oleic acid was impaired for 4 weeks. Ten dogs with severe short bowel syndrome but intact ileocaecal valve were maintained in good health for more than 7 months by a 100 cm ileal autograft.

Keywords: Ileum, autograft

Transposition of a segment of jejunum to provide a substitute for the oesophagus was initially suggested by Wullstein in 1904[1] and 3 years later Roux[2] performed this operation for the first time on a child suffering from a benign stricture of the oesophagus. The upper small intestine subsequently became widely used for oesophageal replacement and has also been used for replacement of the ureter, bladder, biliary tract and for pancreatic drainage.

Recent advances in microsurgical techniques have allowed the use of free intestinal autografts with heterotopic microvascular reanastomosis in the neck[3] for oesophageal replacement when reconstruction by intestinal transposition would be impossible. Intestinal autografts function adequately as an oesophageal substitute[4] allowing passage of solids and liquids, but their morphology, motility and absorptive function have never been studied in detail.

Interest has recently been rekindled in intestinal allografting as a means of treating patients with the short bowel syndrome and a number of studies[5,6] in animals support the feasibility of the procedure if antirejection therapy can be improved. Little is known, however, of the long-term function of small intestinal transplants and the length of intestinal graft required to maintain adequate nutrition has not been defined.

The aim of this study was to determine the effect of autotransplantation of a 100 cm segment of terminal ileum on its absorptive and motor function and to discover if absorption from the autograft alone was sufficient to maintain dogs in good health indefinitely.

Materials and methods

The study was planned from the outset as a three-stage procedure with 10 of the 24 dogs proceeding through all three stages of the experiment.

Stage 1, autotransplantation as a Thiry–Vella segment, was designed to allow easy access to the bowel for the measurement of intestinal motility and absorption by direct methods. Stage 2, restoration of intestinal continuity, was to allow maximal functional recovery of the transplanted bowel before induction of the short bowel syndrome by excision of all non-transplanted intestine at stage 3 of the procedure.

Motility and absorption studies were not performed in stages 2 and 3 of the experiments to avoid the necessity for chronic intestinal cannulation in the conscious animal.

Stage 1

In 24 healthy outbred dogs, a 100 cm segment of ileum was isolated and mobilized completely, based on a terminal branch of the superior mesenteric artery and vein (*Figure 1a*). The distal transection was 2–3 cm proximal to the ileocaecal valve, and continuity of the remaining small intestine was restored by end-to-end anastomosis (*Figure 1b*). The artery and vein to the isolated segment were cross-clamped and divided and the segment completely removed from the animal. The artery of the graft was cannulated and perfused with 500 ml Ringer's lactate containing 10 ml 1 per cent lignocaine and 2000 units heparin at 4°C. Each dog was then given an intravenous infusion of Dextran 70 (20 ml/kg) over 30 min. The intestinal autograft was reimplanted *in situ* by re-anastomosis of the divided superior mesenteric artery and vein using 8/0 Ethilon sutures. Removal of the vascular clamps produced a prompt restoration of circulation to the graft with vigorous peristalsis. The mean ischaemia time was 77 min (range 65–93 min). The mesentery of the graft was then sutured to the adjacent small intestinal mesentery to prevent rotation at the vascular anastomoses. Each end of the autografted ileum was brought out as a stoma on the dog's abdominal wall. In two animals monopolar silver-wire electrodes were attached to the serosal surface of autografted and adjacent non-grafted small intestine at 10 cm intervals. These electrodes were connected to a 12-pin plug set in a stainless steel cannula in the dog's abdominal wall. All animals were given oral neomycin 500 mg twice daily for 2 days before the operation and 250 mg cefuroxime IM at operation and twice a day for 5 days thereafter.

There were six technical failures: in one dog the small size of the mesenteric vessels precluded satisfactory reanastomosis; one dog bled to death from the anastomosis at 24 h after operation and in four animals the graft infarcted as a result of arterial (two dogs) or venous (two dogs) thrombosis.

Perfusion of the lumen of the autografted intestine was performed in six dogs on days 2, 4, 6, 8, 10, 14 and 28 after grafting. Before each experiment, the dog was fed a standard meal of 300 g Go-Dog pellets (Carnation Ltd) to induce the fed pattern of intestinal electrical activity, and placed in a restraining harness for the duration of the experiment. The autografted segment was flushed of debris using 300 ml of a solution of 100 mM glucose and 90 mM NaCl (osmolality 265 mosmol/l) maintained at 38°C in a water bath. The segment was then perfused with the same solution to which was added 1 mmol L-alanine, 1 mmol lauric acid (C:10) dissolved in 10 ml 10 per cent Ox Bile (Dessicated Ox Bile: Oxoid Ltd, UK) and 0·5 mmol medium chain triglycerides (10 per cent MCT; B. Braun, Melsungen, FRG). This solution had an osmolality of 284 mosmol/l and a mean pH of 5·8 (range 5·4–6·1). In six animals not proceeding to stage 2, oleic acid (C:18 unsaturated) was substituted for lauric acid to study long chain fatty acid absorption. The solution was infused at 2·9 ml/min and the effluent collected from the distal stoma. A

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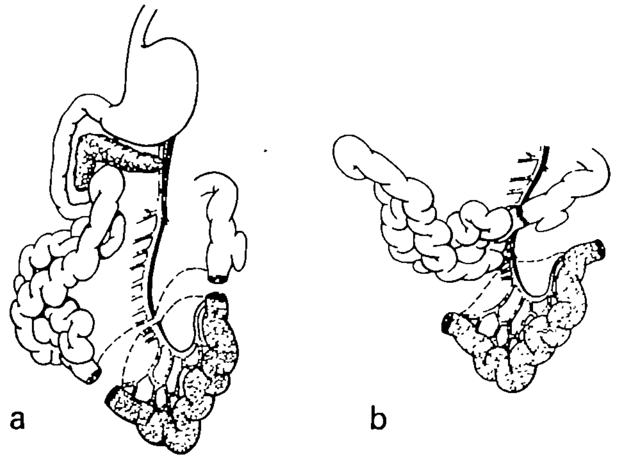

Figure 1 *Method of canine autotransplantation: stage 1.* **a** *Removal of ileal segment on vascular pedicle of superior mesenteric vessels.* **b** *Orthotopic autotransplantation as a Thiry–Vella segment and restoration of intestinal continuity*

30 min stabilization period was allowed and collections were then made at 5 min intervals for a further 60 min.

Effluent volumes were recorded and their sodium and glucose concentrations measured by automated flame photometer and glucose oxidase methods respectively. Free fatty acid (FFA) concentrations in perfusate and effluent were determined enzymatically by the method of Shimizu *et al.*[7]. Triglycerides were also measured enzymatically using Sigma Kit No: 335-2. Alanine was measured by a modification of the method of Williamson[8].

A trace amount of a non-absorbable marker [^{57}Co] cyanocobalamin (Amersham International) was added to the perfusion solution so that absorption could be calculated from the difference in marker concentration between the input fluid and the effluent. Transit time through the segment was measured by injecting a 0·3 ml bolus of [^{58}Co]-labelled cyanocobalamin (Amersham International) into the proximal stoma and determining the time to 50 per cent recovery in the effluent.

In animals with implanted electrodes, electrical activity was recorded using a Grass polygraph with a time constant of 0·45 s for pacesetter potential recordings and 0·015 s for action potentials.

The intraluminal pressures were recorded by a Grass polygraph from a pressure transducer (PDCR 75 physiological pressure transducer, Druck Ltd, Groby, Leicestershire, UK, attached to the infusion catheter. Pressure tracings were analysed to determine basal intraluminal pressure, the number of peaks of pressure greater than 50 cmH$_2$O, and the number of periods per hour of intraluminal pressure activity.

Multiple mucosal biopsies were taken from 6 to 7 cm inside the proximal and distal stomas on days 2, 4, 6, 8, 10, 14 and 28 and placed in 10 per cent buffered formalin. All animals were weighed pre-operatively and on alternate days thereafter. Results are expressed as mean ± s.e.m. and compared by Student's *t* test for unpaired data unless otherwise stated.

Stage 2

Five to six weeks after intestinal autografting a second stage operation was performed in 10 dogs. The stomas were freed from the abdominal wall and resected back to healthy bowel. The anastomosis for the restoration of intestinal continuity was resected and the dogs' original anatomy restored by end-to-end anastomosis (*Figure 2*).

Stage 3

Two to three months after the stage 2 operation all 10 animals were operated on again. All the non-transplanted small intestine from the duodenum to the transplant was resected (*Figure 3a*) and continuity restored by end-to-end duodeno-ileal anastomosis (*Figure 3b*). At the completion of this operation the total length of small intestine remaining in the dog comprised the first and second parts of the duodenum, 100 cm of autotransplanted ileum and 2–3 cm of ileum proximal to the ileocaecal valve.

Results

Postoperative course

The stomas of successful intestinal autografts were initially oedematous but, after the first 2 days, became increasingly healthy in appearance, bled freely when biopsied and produced clear secretions. In four dogs graft infarction occurred and in these animals the intestinal stomas became cyanosed and oedematous, followed 12–24 h later by obvious necrosis and the appearance of a blood-stained effluent. After both the initial intestinal autograft and the second operation to restore intestinal continuity through the ileal autograft, dogs passed soft stools for about 4–5 days after which faecal consistency returned to normal. After the third operation when almost all of the non-transplanted intestine was resected, all the dogs developed persistent diarrhoea for 3–4 weeks, but then stool consistency improved although remaining loose in all animals. All the dogs subjected to the second and third operations survived for more than 7 months in good health and were then killed.

Weights

The weight of all dogs fell slightly after each operation but mean weights were not significantly lower than pre-operatively after either the first or second operations (96·5 ± 0·5 per cent mean ± s.e.m. at 3 weeks: 96·1 ± 0·7 per cent at 10 weeks). After the third operation the dogs' weights fell by about 10 per cent of their weight before this operation (10 weeks 96·1 ± 0·7 per cent; 20 weeks 87·7 ± 0·6 per cent, $n = 10$; $t = 9·2248$; $P > 0·0001$). This weight loss was never regained, but after recovery from the operation their weights stabilized and all animals remained healthy with good appetites.

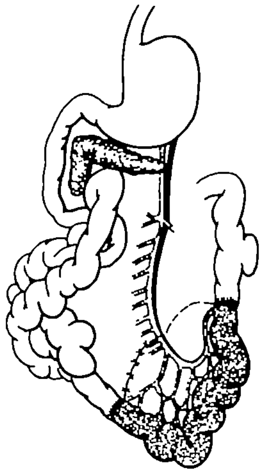

Figure 2 *Stage 2. Restoration of intestinal continuity through the autografted ileal segment*

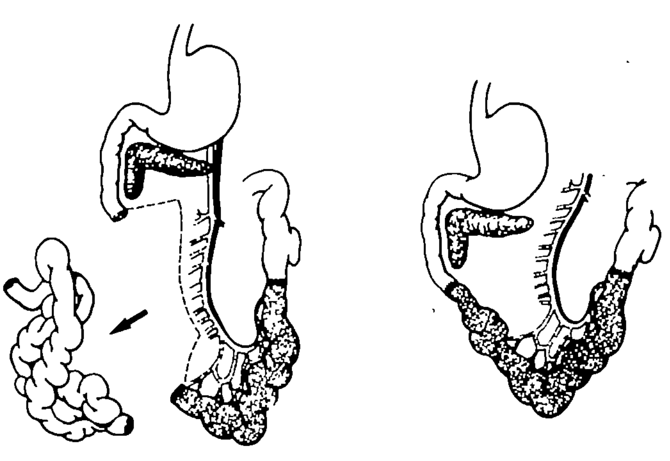

Figure 3 *Stage 3.* **a** *Resection of all non-transplanted small intestine.* **b** *Anastomosis of duodenum to ileal autograft*

Histology

Initially after the stage 1 operation all grafts showed necrosis affecting the tips of some villi side by side with normal intact mucosa. Lacteal vessels were often dilated and goblet cells prominent. These changes although variable in degree were present in all specimens up to the tenth day after autografting. After day 10, however, histology was usually indistinguishable from pre-operative appearances. At post-mortem examinations 6 months after the restoration of intestinal continuity, mucosal histology of the autografted intestine was completely normal.

Motility

Transit times (Figure 4a). Transit times (min) fell from day 2 (28·6±1·8 mean±s.e.m.) to day 4 (15·9±2·4; $t=4{\cdot}19$, $P=0{\cdot}002$) and further to day 6 (7·0±0·9), compared with day 4 ($t=3{\cdot}48$, $P=0{\cdot}006$). Transit times increased again from day 10 (7·7±1·2) to day 14 (14·7±2·2; $t=2{\cdot}75$, $P=0{\cdot}02$). There was, however, no further significant increase to day 28.

Peaks of intraluminal pressure (Figure 4b). The number of pressure peaks per hour greater than 50 cmH_2O increased from day 2 (12·2±2·2 mean±s.e.m.) to day 4 (59·0±8·5; $t=5{\cdot}33$, $P=0{\cdot}0003$) and further increased to day 10 (113·0±10·9) compared with day 4 ($t=3{\cdot}89$, $P=0{\cdot}003$).

Periods of intraluminal pressure activity (Figure 4c). The number of periods of pressure activity per hour increased from day 2 (2·2±0·6 mean±s.e.m.) to day 8 (10·3±1·3; $t=5{\cdot}58$, $P=0{\cdot}0002$) but there was no significant further change.

Myo-electrical activity

Pacesetter potentials and action potentials were present from the time of the first electrical recordings on the second day after autotransplantation. There was no change in the pattern of myo-electrical activity throughout the whole of the postoperative period.

Absorption from the autograft

Oleic acid (Figure 5a). Oleic acid absorption was poor until week 4 when a marked increase in the percentage absorption occurred (week 3: 6·4±2·0 per cent mean±s.e.m.; week 4: 37·0±5·3 per cent; $t=5{\cdot}4$, $P=0{\cdot}0003$). There was a further increase in absorption to week 5 (65·0±2·7 per cent) compared with week 4 ($t=4{\cdot}47$, $P=0{\cdot}0008$).

Lauric acid. There was an increase in the percentage absorption of lauric acid from day 2 (18·6±2·5 per cent mean±s.e.m.) to day 6 (30·5±3·0 per cent, $t=3{\cdot}06$, $P=0{\cdot}01$). There was no significant change in absorption after day 6.

Triglyceride absorption (Figure 5b). Triglyceride absorption increased from day 2 (30·2±1·0 per cent mean±s.e.m.) to day 6 (53·3±2·4 per cent; $t=3{\cdot}68$, $P<0{\cdot}006$) but decreased from day 14 (46·7±4·6 per cent) to day 28 (30·6±5·2 per cent; $t=2{\cdot}57$, $P<0{\cdot}02$).

Alanine absorption. There were no significant changes in alanine absorption between the 2nd and 28th day after autotransplantation. The mean absorption of alanine was 31·7±3·4 per cent (mean±s.e.m.) of the amount infused.

Volume of water absorbed (Figure 5c). Water absorption calculated by subtraction of effluent volume from perfusate volume was always slightly higher than calculated absorption, derived from the dilution of a radiolabelled non-absorbable marker. There was a high correlation between the two methods of calculating absorption ($r=0{\cdot}956$, $P=0{\cdot}0008$). Volume absorption by subtraction (ml/5 min) increased from day 2 (3·7±1·1 mean±s.e.m.) to day 8 (8·2±0·8; $t=3{\cdot}32$, $P<0{\cdot}008$) but subsequently decreased to day 28 (5·2±0·09; compared with day 8 ($t=2{\cdot}60$, $P<0{\cdot}03$)).

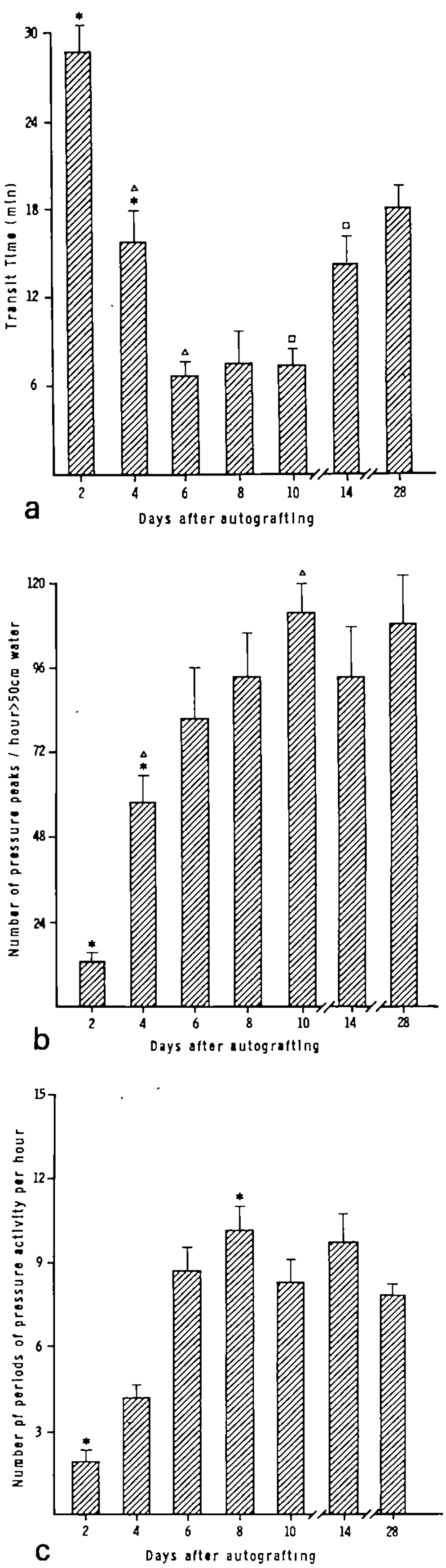

Figure 4 **a** *Transit times, i.e. time to 50 per cent recovery of* ^{58}*Co from autotransplanted ileal segments: histogram shows mean*±*s.e.m.,* n=*6,* *P<*0·005,* △ P<*0·01,* □P<*0·05.* **b** *The number of peaks per hour of intraluminal pressure* >*50 cm*H_2O *in autotransplanted ileal segments; histogram shows mean*±*s.e.m.,* n=*6,* *P=*0·0003,* △ P=*0·003.* **c** *The number of periods per hour of intraluminal pressure activity in autotransplanted ileal segments; histogram shows mean*±*s.e.m.,* n=*6,* *P=*0·0002*

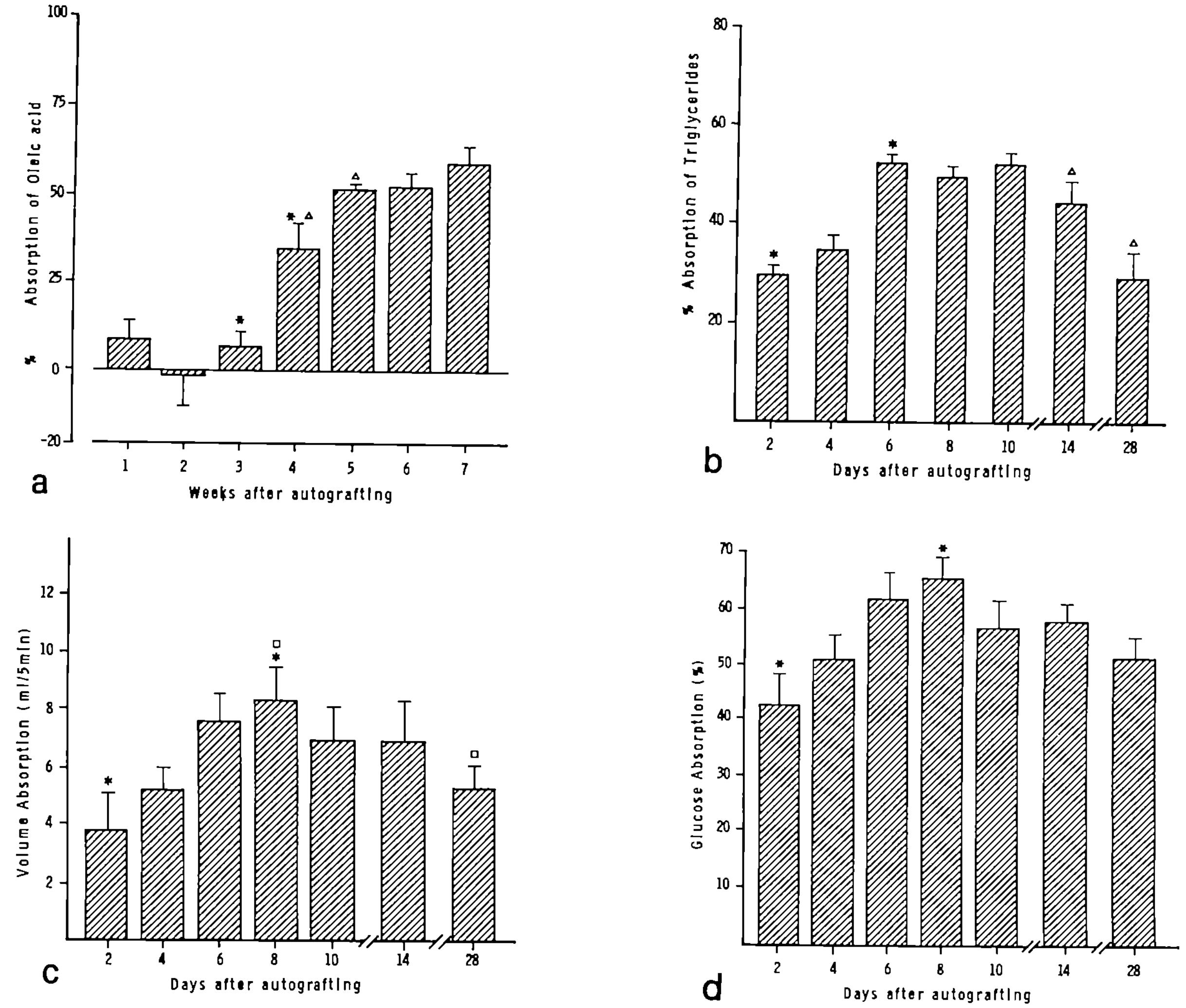

Figure 5 *Absorption from autotransplanted ileal segments. All values mean ± s.e.m.; n = 6.* **a** *Oleic acid; *P<0·001, △ P<0·001.* **b** *Medium chain triglyceride; *P<0·0001, △ P<0·02.* **c** *Water absorption from autotransplanted ileal segments perfused at 14·5 ml/5 min; *P<0·001, □ P<0·05.* **d** *Glucose; *P<0·03*

Sodium absorption. Absorption increased from day 2 (18·1 ± 9·7 per cent mean ± s.e.m.) to day 8 (49·6 ± 6·0; $t = 2{\cdot}76$, $P = 0{\cdot}02$).

Glucose absorption (Figure 5d). Glucose absorption increased from day 2 (42·1 ± 7·6 per cent mean ± s.e.m.) to day 8 (64·1 ± 2·4 per cent, $t = 2{\cdot}47$, $P < 0{\cdot}03$).

Discussion

Carrel, in 1906[9], was the first to describe autotransplantation of a loop of small intestine into the neck of a dog 'as a preliminary study of the substitution of such a tube for the oesophagus'. The intestinal vessels were anastomosed to the carotid artery and jugular vein and the intestine immediately achieved normal colour and peristalsis. In 1959, Seidenberg *et al.*[10] reported the first successful intestinal autotransplant in man when they used a segment of jejunum to replace an oesophagus resected for recurrent carcinoma.

Experimental small intestinal autotransplantation was studied in detail by Lillehei *et al.*[11]. They autografted the entire small intestine of dogs after various periods of storage *in vitro*. The animals had severe diarrhoea and steatorrhoea for 1 week, but by 3 weeks normal appetite had returned and the dogs began to gain weight. By 4–6 weeks the stools were normal and lymphatic regeneration had occurred. Surviving dogs were studied for up to 7 years during which time they remained in good health with normal intestinal motility and mucosal histology.

Our experiments show that a 100 cm ileal autograft is sufficient for adequate nutrition in the dog. The animals can be maintained at 90 per cent of their pre-operative weights with an autograft of 25 per cent of the total small intestinal length. The ileocaecal valve remained intact and there was only slight softening of stool consistency after the dogs had recovered from their operations.

Intestinal ischaemia times of up to 93 min were well tolerated and intestinal function soon recovered after the operation. Improvement in function as measured by increased absorption of water, electrolytes, carbohydrates, amino acids and short chain fatty acids was accompanied by increased mechanical activity of the intestine and was maximal by day 8. The return of motility is probably partly responsible for the increase in absorption as a consequence of better mixing of intraluminal contents. The gradual return of mechanical activity did not correspond with any change in myo-electric activity which was normal from the second day after transplantation.

Absorption of the long chain fatty acid, oleic acid, did not start to recover until the fourth week after intestinal autografting. This long delay is likely to be a consequence of the time taken for lymphatic regeneration to occur. The problem has been studied by Kokandrie *et al.* in 1966[12] who visualized the lymphatic pathways by subserosal injection of Evans blue dye and by direct lymphangiography. They found that lymphatic channels first crossed the suture line from the mesentery of the transplanted intestine to the host mesentery within 2 weeks and their size steadily increased until development was complete by 4 weeks after grafting.

Denervation is thought to affect morphology and function of the intestine. In 1962, Ballinger *et al.*[13] showed that autotransplantation of the entire small intestine in the dog produced loss of weight, diarrhoea, impaired absorption of fat, radiological abnormalities and flattening of the mucosa with a reduction in villus height. Some of these changes did not return completely to normal for up to 6 months. They also demonstrated that the changes were not the result of acute or chronic ischaemia, but claimed that intestinal denervation produced similar effects. Although not commented on by these authors it is apparent that the technique of denervation used would also have produced complete interruption of lymphatic venous drainage of the intestine and it seems likely that most, if not all, of the changes observed were a consequence of lymphatic interruption. The weight loss and diarrhoea caused by impaired fat absorption observed by Ballinger *et al.*[13] after total small intestinal autografting did not occur in our dogs until all their non-transplanted small intestine was removed at the stage 3 operation 2–3 months after segmental intestinal autotransplantation.

In our studies the morphological appearances of the intestinal mucosa in the first few days after autografting were characterized by superficial epithelial sloughing, cellular infiltrates, lacteal vessel dilatation and goblet cell prominence. Similar changes have been attributed by others to allograft rejection[14] indicating that caution should be exercised in the diagnosis of allograft rejection using these criteria. The morphology of the intestinal autograft mucosa had returned to normal by day 10 and this corresponds to the maximal recovery of intestinal absorption and mechanical activity.

The early appearance of myo-electrical activity in our animals confirms the findings of Bueno *et al.* in 1978[15] who showed that action potentials return within 25 h of surgical trauma. Furthermore, the progressive return of organized mechanical activity in intestinal autografts supports the finding of Sarr and Kelly in 1981[16] that extrinsic nerves to segments of jejuno-ileum are not necessary for the appearance of the interdigestive myo-electrical complex.

Our experiments have shown that orthotopically vascularized 100 cm segmental ileal autografts can be carried out in dogs with a high degree of technical success. The myo-electrical activity of the segment is not disturbed by transplantation while mucosal histology, motor function and absorptive capacity have almost fully recovered within 10 days of grafting. These findings would support the investigation of the segmental ileal allograft as an appropriate method of treatment for the short bowel syndrome.

Acknowledgements

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Single dose antibiotic prophylaxis in high risk patients undergoing transurethral prostatectomy

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In a randomized controlled clinical trial single dose antibiotic prophylaxis (gentamicin 80 mg IV) was evaluated in 36 patients with in-dwelling urethral catheters undergoing transurethral prostatic resection. Prophylaxis resulted in a significant reduction in postoperative bacteriuria ($P<0{\cdot}01$), *pyrexia* ($P<0{\cdot}001$), *bacteraemia* ($P<0{\cdot}01$) *and septicaemia* ($P<0{\cdot}05$). *During the same period there was one case of postoperative bacteriuria but no systemic infection in 25 consecutive patients undergoing elective prostatectomy with no local risk factors and in the absence of prophylaxis. A policy of selective antibiotic prophylaxis is justified and in high risk patients with in-dwelling catheters single dose prophylaxis is highly effective.*

Keywords: Prostatectomy, antibiotics, prophylaxis

Recent controlled trials have shown that single dose antibiotic prophylaxis significantly reduces infective complications following transurethral prostatectomy and authors advocate a policy of antibiotic prophylaxis for all patients undergoing transurethral resection of the prostate[1–3]. Closer analysis of treatment and control groups in these studies suggests that patients with in-dwelling urethral catheters before surgery have a high risk of developing infective complications postoperatively. In this study the efficacy of single dose prophylaxis specifically in this 'high risk' group was assessed and the need for prophylaxis in the absence of local risk factors was evaluated.

Patients and methods

Thirty-six consecutive patients with in-dwelling urethral catheters before surgery were randomly allocated to treatment (group 1) or control (group 2) (*Figure 1*). All patients had required catheterization for acute urinary retention. The treatment group received 80 mg gentamicin intravenously following induction of anaesthesia and before urinary tract instrumentation.

During the same study period 25 consecutive patients admitted for elective operation with no local predisposing risk factors (group 3) were evaluated for infective complications postoperatively. They did not receive antibiotic prophylaxis. Patients with evidence of chronic retention or urinary tract infection, including patients treated for urinary tract infection within 2 weeks of surgery, were excluded from this 'cold' elective prostatectomy group.

Catheter specimens of urine were taken from all catheter patients and mid-stream urine specimens from the 'cold' elective group on the morning of surgery and submitted to the laboratory for culture and sensitivity tests.

A catheter specimen of urine was taken postoperatively before catheter removal, which was usually on the second postoperative day, and a mid-stream urine specimen was obtained 24 h after catheter removal. Peripheral blood culture specimens were obtained from all patients within 30 min of completion of surgery and also postoperatively when clinically indicated (blood pressure < 100 mmHg, pyrexia > 37·5°C, or rigors).

The three groups were similar in terms of patient age and groups 1 and 2 were similar in terms of duration of catheterization and number of patients with significant bacteriuria or mixed contaminants before surgery (*Table 1*).

In the laboratory, using a standard loop, one microlitre of urine was plated on cysteine lactose electrolyte deficient agar (CLEDA) and cultured for 24 h at 37°C. Significant bacteriuria was defined as $>1\times10^8$ of a single organism/litre. Where growth of > 100 colonies of two or more organisms occurred the specimen was reported as containing 'mixed contaminants'.

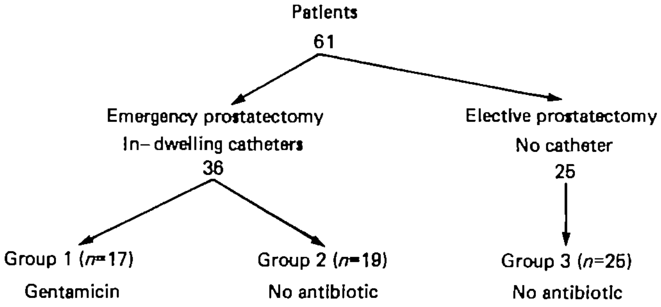

Figure 1 *Outline of study*

Blood culture specimens were incubated overnight and subcultured the following morning onto blood agar and 'chocolate' agar plates. The plates were then incubated in both aerobic (5 per cent CO_2 in air) and anaerobic environments and examined at 24 and 48 h. Blood culture specimens were also subcultured for 3 consecutive days following original overnight incubation.

Postoperative bacteraemia was defined as the isolation of an organism from peripheral blood obtained within 30 min of surgery. Postoperative septicaemia was defined as the presence of clinical features (blood pressure < 100 mmHg, pyrexia > 37·5°C, or rigors) together with a positive blood culture. Statistical analysis was carried out using Fisher's exact test of probability.

Results

Postoperative bacteriuria

Patients with in-dwelling catheters before surgery who did not receive prophylactic antibiotics (group 2) had a higher incidence of significant bacteriuria before catheter removal ($P<0{\cdot}01$) and again 24 h following catheter removal ($P<0{\cdot}05$) (*Table 2*). Of 25 patients undergoing elective prostatectomy, only one case of postoperative bacteriuria was identified 48 h after operation.

Postoperative systemic complications

Patients with in-dwelling catheters before surgery who did not receive antibiotic prophylaxis had a significantly higher incidence of postoperative bacteraemia ($P<0{\cdot}01$), postoperative pyrexia ($P<0{\cdot}001$) and postoperative septicaemia ($P<0{\cdot}05$) (*Table 2*).

Of 25 patients undergoing elective prostatectomy no case of

Table 1 *Relationship of pre-operative urine culture to postoperative infective complications in patients with in-dwelling catheters before surgery*

	Pre-operative urine culture in patients with in-dwelling catheters					
	No growth ($n=7$)		Mixed contaminants ($n=8$)		Significant growth ($n=21$)	
Postoperative infective complications	Group 1 (4)	Group 2 (3)	Group 1 (5)	Group 2 (3)	Group 1 (8)	Group 2 (13)
Postoperative bacteriuria						
48 h	0	0	0	1	1	8
24 h after catheter removal	0	0	0	2	1	5
Postoperative						
Pyrexia 37·5°C	0	0	0	3	2	9
Bacteraemia	0	1	1	2	0	5
Septicaemia	0	0	0	2	1	4

Table 2 *Postoperative infective complications in patients undergoing emergency or elective prostatectomy*

	Emergency (in-dwelling catheter)		Elective
	Treatment group 1 ($n=17$)	Control group 2 ($n=19$)	Control group 3 ($n=25$)
Bacteriuria 48 h postoperatively	1	9†	1
Bacteriuria 24 h postcatheter removal	1	7*	0
Postoperative pyrexia >37·5°C	2	12‡	0
Postoperative bacteraemia	1	8†	0
Postoperative septicaemia	1	6*	0

$^{*}P<0{\cdot}05$, $^{\dagger}P<0{\cdot}01$, $^{\ddagger}P<0{\cdot}001$

bacteraemia or septicaemia was recorded despite the fact that such patients did not receive antibiotic prophylaxis.

The relationship of pre-operative urine culture to postoperative infective complications, local and systemic, is outlined in *Table 1*. All patients in group 3 had sterile urine before surgery, and, apart from a single case of postoperative bacteriuria which resolved on catheter removal, had no postoperative infections. Of 36 patients with in-dwelling catheters 7 had sterile urine before surgery (4 in group 1), 8 showed a growth of mixed contaminants (5 in group 1), and the majority, 21, had significant growth of a single organism (8 in group 1). Of seven patients with sterile urine before surgery no case of bacteriuria and only one case of bacteraemia occurred postoperatively; the single bacteraemia occurring in one group 2 patient who did not receive antibiotic prophylaxis. Of eight patients with mixed contaminants identified in the urine before surgery three postoperative bacteriurias (one before and two after catheter removal), three bacteraemias and two septicaemias developed following operation, all complications except one bacteraemia occurring in group 2 patients not receiving prophylaxis. Of 21 patients with a significant growth of a single organism identified in the urine before surgery 15 cases of postoperative bacteriuria (9 before and 6 following catheter removal), 11 pyrexias, 5 bacteraemias and 5 septicaemias developed after operation: two postoperative bacteriurias, two pyrexias and one septicaemia (*Staphylococcus aureus*) occurred in group 1 patients receiving prophylaxis.

The organisms isolated from blood and urine cultures were *Escherichia coli* 23 (18 urine), *Staphylococcus aureus* 14 (8 urine), *Staphylococcus albus* 6 (all urine), *Proteus mirabilis* 4 (all urine) and *Klebsiella* 4 (3 urine). The single case of systemic infection in 17 group 1 patients receiving gentamicin peroperatively was due to a *Staphylococcus aureus* strain resistant to gentamicin. In retrospect a similar strain *Staphylococcus aureus* organism had been isolated in the pre-operative urine specimen from this patient. *Staphylococcus aureus* was also isolated from blood cultures of five patients in group 2 and again these organisms had been identified in pre-operative catheter specimens of urine from these five patients. All five were sensitive to gentamicin. All other organisms isolated during the study were sensitive to gentamicin.

Discussion

Single dose antibiotic prophylaxis is simple, inexpensive and unlikely to lead to super-infection, drug toxicity or the emergence of resistant strains. The aim of administering antibiotic prophylaxis to at-risk patients is to achieve effective antibiotic levels in the blood at the time of maximum bacterial contamination. Patients with in-dwelling catheters before surgery are reported to be at greater risk of developing infective complications postoperatively but no study to date has evaluated single dose antibiotic prophylaxis specifically in this group[1]. This study confirms the high risk nature of such patients and clearly demonstrates the efficacy of single dose gentamicin when given intravenously to those patients before urinary tract instrumentation.

Gentamicin was chosen as the antibiotic of choice because a retrospective analysis of organisms isolated from patients undergoing prostatectomy in this unit in the previous 12 months showed gentamicin to be the antibiotic with the most suitable range of antibacterial activity. Whilst we were aware of the risks of gentamicin, particularly in patients with impaired renal function, the administration of a single dose in this and other studies[4] did not appear to have any nephrotoxic or neurotoxic side effects. The single systemic infection that developed despite gentamicin prophylaxis was due to a resistant strain of *Staphylococcus aureus*, which was present in the catheter specimen of urine obtained pre-operatively. Perhaps a policy of obtaining the result of the urine culture before surgery and administering an appropriate antibiotic in each case would have prevented any postoperative systemic infections.

Antibiotic prophylaxis in this study refers to protection against systemic infection and not local urinary tract infection since 29 of 36 patients already had bacteriuria before surgery. The study demonstrates that even in the presence of pre-operative bacteriuria single dose prophylaxis eliminates systemic infections postoperatively provided the organism is sensitive. The isolation of mixed bacterial growths from catheter specimens is often thought to be insignificant or to represent contamination, but Gordon *et al.*[5] have emphasized that such growths should not be disregarded and this study supports such a view.

The incidence of infective complications in patients admitted for elective cold prostatectomy was low (4 per cent local, no systemic infections). Low infection rates (3·5 per cent) have been reported previously in a series of non-selected patients following prostatectomy[6]. The majority of recent studies, however, report infection rates >20 per cent in the absence of prophylaxis[3,4]. These studies included patients with in-dwelling catheters before surgery. The low incidence of infection following elective prostatectomy in this study is explained by the deliberate selection of patients who did not have in-dwelling catheters or evidence of chronic urinary retention and whose urine was sterile pre-operatively.

In conclusion this study indicates that a policy of selective antibiotic prophylaxis, as currently practised by 80 per cent of British urologists who responded to a recent questionnaire[7], is justified. The study confirms the high-risk nature of patients with in-dwelling catheters before surgery and demonstrates the value of single dose antibiotic prophylaxis in this group.

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Case report

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Excision of solitary lung metastases from two patients with breast cancer

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Although breast cancer commonly spreads to the lungs, surgical resection of metastatic disease in this site is rarely possible because of the extent of involvement[1–4]. These reports suggest that post-thoracotomy long term survival is unusual with only 15 per cent of patients being alive at 5 years[3,4] probably because of incomplete excision of multiple metastases. In a review of over 1000 patients with metastatic breast cancer, we identified two patients who had excision of solitary lung metastases[5].

Case reports

Case 1

In November 1979 a 68-year-old woman was found to have a solitary nodule on chest X-ray while being followed up after a left mastectomy for breast cancer in April 1976. The solitary nature of the lesion was confirmed on whole lung tomography and other staging investigations (biochemistry, bone marrow, liver isotope scan and ultrasound, bone scan) were all normal. Needle biopsy confirmed adenocarcinoma and lung function tests were normal.

On 30 November 1979 she underwent thoracotomy and right upper lobectomy. Histology of the 2 × 2 × 1·5 cm lesion within the lobe revealed a moderately differentiated adenocarcinoma; there was no evidence of a local origin and appearances were similar to the histology of the breast carcinoma removed in 1976.

Subsequently she has remained well, without treatment or any evidence of further relapse.

Case 2

In December 1976 a 49-year-old woman was found to have a solitary nodule on chest X-ray during follow-up investigations after a right mastectomy for breast cancer in November 1974. The single lesion was confirmed on whole lung tomography which was otherwise normal, as were other staging investigations (see earlier). Needle biopsy of the lesion failed to reveal malignant cells.

On 18 February 1977 a thoracotomy was performed and a 1·5 cm spherical nodule, together with a margin of normal lung, was excised from the axillary basal segment of the right upper lobe. Histology revealed a partly necrotic adenocarcinoma closely resembling the primary breast carcinoma removed in 1974.

In February 1982 she underwent wide excision of a lump in the left breast. Histology showed an infiltrating carcinoma which, when compared histologically to the previous tumour, indicated a new primary carcinoma. No further treatment was required for this cancer and, to date, there is no evidence of recurrence or further metastases.

Discussion

Although excision of lung metastases is rarely performed in breast cancer, the long term relapse-free survival after thoracotomy in these two patients (over 6 and 9 years respectively) suggests that the procedure may sometimes be indicated. Furthermore, when needle biopsy is unhelpful (as in case 2), diagnostic thoracotomy may be required, as solitary lung nodules are metastatic in only 32 per cent of patients who have previously had primary breast cancer. However, the occurrence of solitary lung metastases in breast cancer is rare; we have seen it only twice in over 1000 patients with metastatic breast cancer[5].

Apart from the solitary nature of the metastatic disease and its surgically accessible location, the major indicators of good prognosis[5] in both these patients were the relatively long disease free intervals (25 and 43 months compared to the median of 15 months in our series[5]) and the histopathological grade of both primary tumours, which was grade II and not grade III.

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Accuracy of suture placement

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Three groups of seven surgeons were each randomly selected from three larger groups with surgical experience of <1, 6–10 and 16–20 years. Each surgeon was asked to aim a needle at an exit point using two methods: 'jiggling' (readjustment of the needle in aiming at the target) allowed and jiggling not allowed. The results were not as precise as expected. An improvement from group 1 to group 2 was noticed in both methods ($P < 0.01$), but from group 2 to 3 there was improvement only in the method where jiggling was allowed ($P < 0.01$). All groups showed a tendency to overshoot the target ($P < 0.01$): a shift towards the surgeon in group 1 ($P < 0.05$) and towards the opposite side in groups 2 ($P < 0.01$) and 3 ($P < 0.05$). Jiggling significantly reduced the inaccuracy, and it was concluded that pinpoint accuracy improved with surgical experience. However, the experienced surgeons improve their accuracy by jiggling, with the potential danger of tissue damage by needle adjustment.

Keywords: Sutures, needle placement, surgical technique

In the surgical literature suturing is only referred to under the heading of materials and the technique of handling a needle has never been investigated to my knowledge. Although sutures are a basic requirement in nearly all operations, more information is required concerning the technique surgeons use. This study was instigated to investigate one aspect of the neglected field of surgical technology: the preciseness of suture technique in surgeons of varying experience from major hospitals.

Subjects and methods

Twenty-one surgeons were randomly selected from three larger groups with surgical experience of <1, 6–10 and 16–20 years, respectively. There were seven surgeons in each group. They passed a suture through two points, one for entry, the other exit, marked on Japanese paper fixed to an embroidery frame 18 cm in diameter. The points were situated 2 cm apart, on the assumption that a half-circle type needle with a diameter of 29 mm produces a 2 cm span with a 90° rotation usually employed in suturing ($\text{span} = \sqrt{2} \times \text{radius} = \sqrt{2} \times 29/2 = 20{\cdot}5$ mm). Surgeons often waver a needle to improve the accuracy of placement after suture is started. We term this 'wavering' or 'jiggling'. Twenty-two attempts were allowed with each of the two methods: an adjustment by 'jiggling' the tip and no adjustment. Each row contained eleven pairs of points, and surgeons sutured two rows with and two without jiggling. The method of holding the 18 cm needle holder (Hegar, model 35–4900, Pilling, FRG), or embroidery frame was left to the surgeon. However most used the common grip of thumb and ring finger with the index finger guiding.

The preciseness of suturing was described by the distance and direction of deviation from the exact exit point measured in millimetres. The direction of needle deviation from the expected exit point was measured in rectangular coordinates (*Figures 1–4*). The direction of deviation toward the surgeon's side is shown as negative on the ordinate; shortfall to the point is positive on the abscissa.

The numbers given in *Figures 1–3* are the frequency of needle deviation without jiggling, compared with jiggling in parentheses. The deviation in distance, irrespective of direction, was evaluated with the Mann–Whitney *U* test, after the Krukal–Wallis test. The χ^2 test was used for the difference between each group (i.e. the difference due to experience) and also for the suturing method differences. The Sign test was used for the intra-group differences.

Results

Most exits of the least accurate surgeon without jiggling were in the fourth quadrant, and there was no exit within 2 mm of the expected exit point (*Figure 4*). The deviation from the most accurate surgeons without jiggling was within 2 mm in the third quadrant and on the negative side of the abscissa; with jiggling accuracy was within 1 mm.

In group 1, most deviations without jiggling were directed to the fourth quadrant and were 3–4 mm from the expected exit point (*Figure 1*). Deviations without jiggling were on the negative side of the abscissa but with much less inaccuracy. In group 2, the third quadrant was the most common exit point with 2–3 mm distance from the expected exit point for needles handled without jiggling. With jiggling, deviations were on the negative side of the abscissa and within 1 mm (*Figure 2*). In group 3, for needles aimed without jiggling, most deviations were in the third quadrant and within 1 mm on the negative side of the abscissa. With jiggling they remained within 1 mm and on the negative side of the abscissa (*Figure 3*).

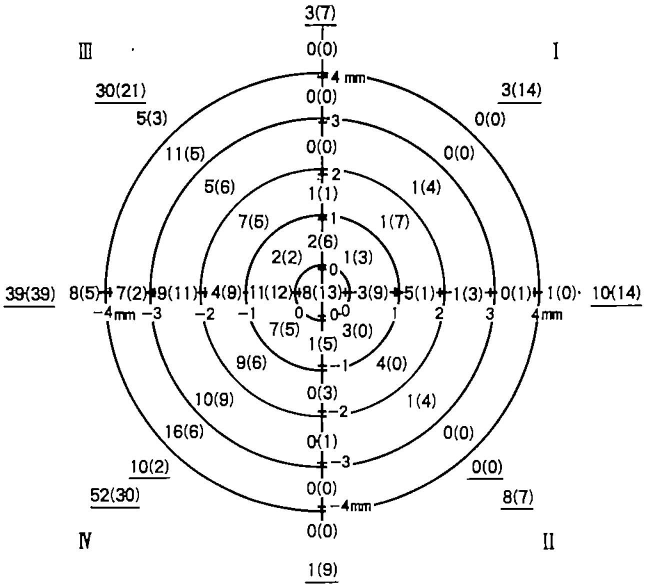

Figure 1 *Needle emergence in surgeons with <1 year of surgical experience. The innermost circle represents the expected place of needle emergence. Negative values on the abscissa mean that the needle overshot the target; negative values on the ordinate mean a drift towards the surgeon's side. Emergence of 154 suturings each with and without jiggling by seven surgeons with surgical experience <1 year were plotted. The numbers give the frequency of needle exits in suturing without jiggling; values in parentheses are for suturing with jiggling*

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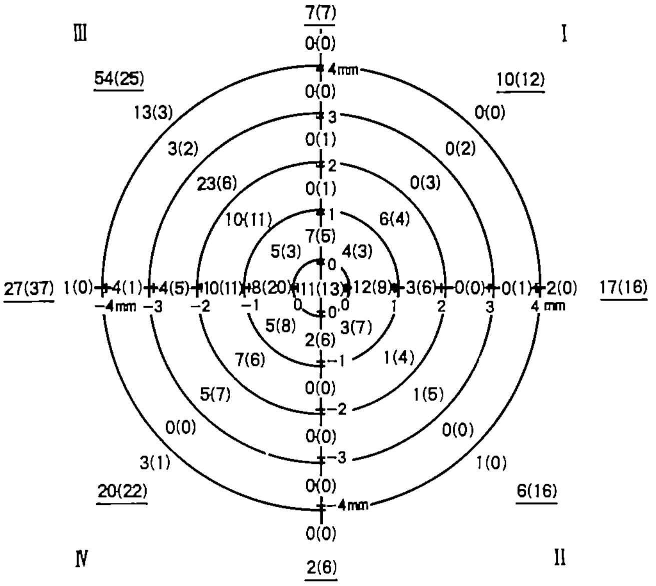

Figure 2 *Needle emergence in surgeons with 6–10 years surgical experience*

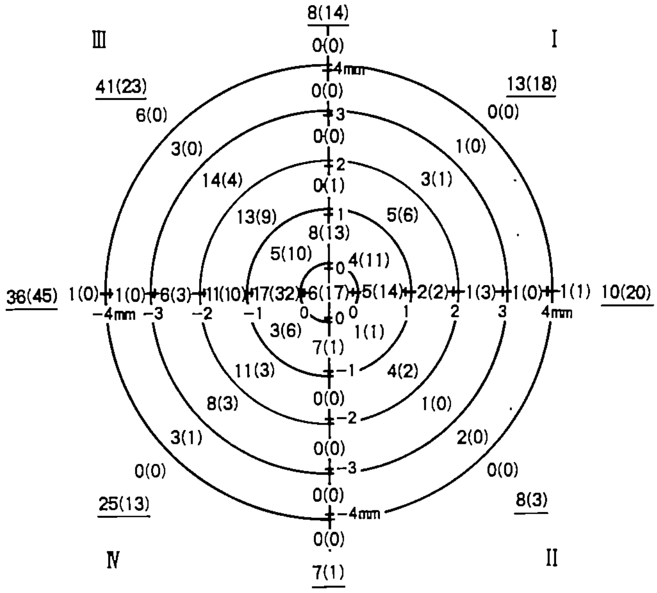

Figure 3 *Needle emergence in surgeons with 16–20 years surgical experience*

In evaluating the accuracy of suturing without jiggling in terms of distance deviated from the expected exit point, neglecting direction, groups 2 and 3 were more accurate than group 1 ($P<0{\cdot}01$) (*Table 1*). There was no significant difference between groups 2 and 3. There was a significant improvement from group 1 to 3 when jiggling was permitted ($P<0{\cdot}01$), in other words as surgical experience increased, and the intra-group precision also improved with jiggling ($P<0{\cdot}01$).

In all groups there was a tendency to overshoot the exit point, with or without jiggling, ($P<0{\cdot}01$), although less so in the former case (*Table 2*). The difference without jiggling was most marked in group 1 when compared with the other two groups ($P<0{\cdot}05$), but this difference disappeared when jiggling was introduced, groups 1 and 3 improving most ($P<0{\cdot}01$ and 0·05, respectively).

The vertical shift observed without jiggling was towards the surgeon in group 1 ($P<0{\cdot}05$) and the opposite side in groups 2 ($P<0{\cdot}01$) and 3 ($P<0{\cdot}05$) (*Table 2*). When jiggling was allowed, this disappeared in groups 1 and 2, and shifted towards the exit point in group 3 ($P<0{\cdot}01$). There was a significant difference between group 1 and groups 2 and 3 without jiggling ($P<0{\cdot}01$), which on jiggling became a difference between groups 1 and 2 compared with 3 ($P<0{\cdot}01$). Jiggling moved the displacement toward the centre in group 2 and 3 ($P<0{\cdot}01$).

Discussion

All surgeons should have a suture technique which enables them to pinpoint a needle's exit from the tissues, thereby reducing possible tissue trauma. The surgeons studied were confident of

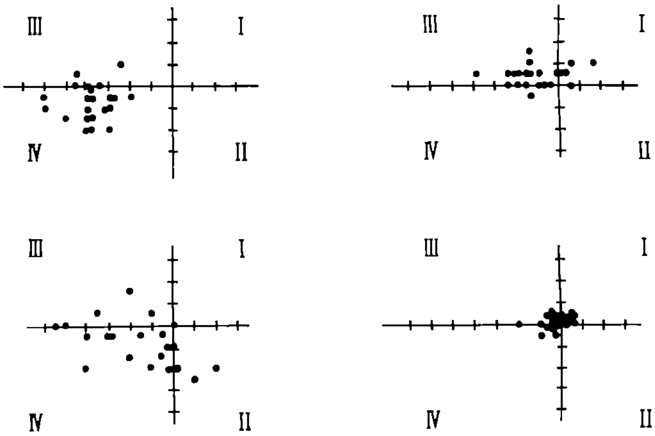

Figure 4 *Needle emergence. Twenty-two suturings, each without (upper diagrams) and with (lower diagrams) jiggling were aimed at the origin of the coordinates with a stride of 2 cm and their emergence was plotted. The left row shows those for a surgeon with <1 year surgical experience whose results scattered the most widely, the right being the least scattered results, a surgeon with 16 years experience. One division indicates 1 mm*

Table 1 *Deviation of needle emergence (frequency table)*

Test	Group	Surgical experience (years)	Deviation, d (mm)						P value
			$d=0$	$0<d\leqslant1$	$1<d\leqslant2$	$2<d\leqslant3$	$3<d\leqslant4$	$4<d$	
Suturing without jiggling	1	<1	8	30	31	27	34	24	*a,b,d*
	2	6–10	11	46	37	33	7	20	*a,c,e*
	3	16–20	6	50	46	33	11	8	*b,c,f*
Suturing with jiggling	1	<1	13	44	35	38	14	10	*g,h,d*
	2	6–10	13	61	43	27	6	4	*g,i,e*
	3	16–20	17	88	33	14	1	1	*h,i,f*

a, <0·01 between groups 1 and 2 without jiggling; *b*, <0·01 between groups 1 and 3 without jiggling; *c*, n.s. between groups 2 and 3 without jiggling; *d*, <0·01 between suturings with and without jiggling in group 1 (intra-group difference); *e*, <0·01 intra-group difference in group 2; *f*, <0·01 intra-group difference in group 3; *g*, <0·01 between groups 1 and 2 with jiggling; *h*, <0·01 between groups 1 and 3 with jiggling; *i*, <0·01 between groups 2 and 3 with jiggling

Table 2 *Propensity of suturing*

			Displacement of needle point (*n*)					
			Horizontal			Vertical		
Test	Group	Surgical experience (years)	over ($-x$)	0	under ($+x$)	above ($+y$)	0	below ($-y$)
Suturing without jiggling	1	<1	121	12	21	36	57	61
	2	6–10	101	20	33	71	55	28
	3	16–20	102	21	31	62	52	40
Suturing with jiggling	1	<1	90	29	35	42	66	46
	2	6–10	84	26	44	44	66	44
	3	16–20	81	32	41	55	82	17

Inter-group difference (difference due to surgical experience)

Suturing without jiggling

Horizontal: $P<0\cdot05$ between groups 1 and 2, $P<0\cdot05$ between groups 1 and 3, n.s. between groups 2 and 3

Vertical: $P<0\cdot01$ between groups 1 and 2, $P<0\cdot01$ between groups 1 and 3, n.s. between groups 2 and 3

Suturing with jiggling

Horizontal: n.s. in any two groups

Vertical: n.s. between groups 1 and 2, $P<0\cdot01$ between groups 1 and 3, $P<0\cdot01$ between groups 2 and 3

Suturing pattern (suturings without and with jiggling in the same group)

Horizontal: $P<0\cdot01$ in group 1, n.s. in group 2, $P<0\cdot05$ in group 3

Vertical: n.s. in group 1, $P<0\cdot01$ in group 2, $P<0\cdot01$ in group 3

Intra-group difference

Suturing without jiggling

Horizontal: $P<0\cdot01$ in each group

Vertical: $P<0\cdot05$ in group 1, $P<0\cdot01$ in group 2, $P<0\cdot05$ in group 3

Suturing with jiggling

Horizontal: $P<0\cdot01$ in each group

Vertical: n.s. in groups 1 and 2 each, $P<0\cdot01$ in group 3

their technique, particularly the most experienced, but I have shown that accuracy was poor. The fact that there is only a small improvement with experience is both surprising and disturbing. When no jiggling was permitted these figures were even worse. If the exit zone is increased to a 2 mm circle then accuracy increases to 25 per cent in group 1, and 33 per cent in the other two groups, which is still remarkably low. Jiggling, although it improved accuracy, introduces a possibility of increased risk of tissue damage.

The precision of experienced surgeons improved with jiggling, and they seem to have developed this technique subconsciously. A reason for this is possibly they are allowing the needle to take the line of least resistance without realizing it. Conscious attention to jiggling should be encouraged.

Suturing Japanese paper cannot be directly compared with the same exercise in living tissues, but it does give a measure of inaccuracy. This study suggests that surgeons should be trained specifically in suturing techniques and practice should continue. This is but one aspect of the more general subject of surgical technology, which includes knot tying and instrument handling, upon which formal training should be established as early as possible in the career of the surgeon.

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Favourable response to conservative surgery for extra-pancreatic gastrinoma with lymph node metastases

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Five patients with the Zollinger–Ellison syndrome who had extra-pancreatic (duodenal or paraduodenal) gastrinoma with lymph node metastases responded favourably to simple excision or mere shelling out of macroscopic tumour. Acid studies, serum gastrin and the secretin test became normal in all cases in the immediate postoperative period and remained so in three of the five patients when tested at 57, 33 and 8 months. The tests became abnormal in two patients when tested 8 and 53 months after surgery, but both patients are currently well-controlled on ranitidine 150 mg b.d. 22 and 65 months respectively after surgery. These results suggest that in patients with extra-pancreatic gastrinoma who have lymph node metastases simple excision of all macroscopic tumours may offer the prospect of long-term control. The place of total gastrectomy in such patients is questioned.

Keywords: Extra-pancreatic gastrinoma, lymph node metastases

The surgical strategy in the Zollinger–Ellison syndrome (ZES) has changed considerably since the advent of H_2 receptor antagonists. Urgent surgery is no longer required and indeed some authors have questioned the need for laparotomy unless medical therapy has failed, or when tumour can be demonstrated with pre-operative investigations[1]. However, recent reports[2–10] indicate that not only solitary duodenal wall tumours but also extra-pancreatic, extra-intestinal gastrinomas may have an excellent prognosis when excised. Most patients in these reports had a total gastrectomy carried out as an additional procedure. We describe five cases with extra-pancreatic (duodenal or paraduodenal) gastrinoma and/or localized metastatic lymph nodes who responded favourably to simple excision or mere shelling out of all macroscopic tumour.

Patients and methods

Case reports

Case 1. A 36-year-old man with a history of a bleeding duodenal ulcer in 1979 developed a recurrent ulcer while on maintenance treatment with ranitidine. ZES was diagnosed on the basis of the pentagastrin test, fasting serum gastrin and secretin stimulation test (*Table I*) and his symptoms were controlled with cimetidine 400 mg q.i.d. and propantheline 15 mg t.i.d. At laparotomy, no lesion was found in the pancreas. However, a solitary 1·5 cm nodule was noted on the surface of the pancreas on the lateral aspect of the second part of the duodenum (*Figure 1*). The nodule was removed and a vagotomy and pyloroplasty performed. Frozen and paraffin section of the nodule revealed endocrine tumour apparently within a lymph node. Immunohistological (Pap-immunoperoxidase) examination revealed positive staining for gastrin only. Acid secretory levels and the secretin test were normal when tested 27 months postoperatively, but the serum gastrin level started to increase when tested at 36 months (*Figure 2*), and at 53 months a marked basal hypersecretion was noted (*Figure 3*). Endoscopy revealed duodenal erosions only. Although the patient was symptom-free, the basal acid hypersecretion and increasing gastrin levels prompted further therapy with an H_2 receptor antagonist (ranitidine 150 mg b.d.) His symptoms are currently well controlled on this regimen.

Case 2. A 22-year-old woman presented in January 1981 with a 2 year history of established duodenal ulcer disease relieved only partially by cimetidine. Acid studies, fasting serum gastrin and secretin test were consistent with the diagnosis of the ZES (*Table I*). CT scan and selective angiography confirmed the presence of a vascular tumour involving the uncinate process of the pancreas and there was also a suggestion of possible diffuse liver metastases. At surgery a large pedunculated tumour arising from the uncinate process and indenting the duodenal wall was found and easily removed (*Figure 1*). The liver was normal macroscopically, and on biopsy.

Histology of the tumour revealed two conjoined encapsulated masses. These contained endocrine tumour intimately admixed with lymphocytes as well as lymphoid follicles with germinal centres suggesting that the tumour was situated within a lymph node. The tumour on immunoperoxidase staining was positive for gastrin, somatostatin and glucagon but negative for vaso-active intestinal peptide. The postoperative course was uneventful, and the patient remains asymptomatic, with normal basal acid secretion and gastrin levels, 5 years after surgery (*Table 1*, *Figures 2* and *3*).

Case 3. A 16-year-old girl presented at the end of 1981 with a perforated duodenal ulcer developing against a background of recent dyspepsia. The perforation was closed and a proximal gastric vagotomy carried out. Postoperatively a tentative diagnosis of the ZES was made based on acid studies, fasting serum gastrin levels and the secretin test (*Table I*). CT scan and selective angiography failed to demonstrate a tumour, and the patient remained well on full-dose cimetidine therapy (1 g/day). Despite this, surgery was carried out a year later to exclude a resectable lesion. A 3 cm tumour and an enlarged lymph node situated in close proximity to the ligament of Treitz was removed with great ease (*Figure 1*).

Histology of the tumour showed an endocrine growth pattern and the capsule was well defined with no adjacent pancreatic tissue and no features to indicate secondary growth within a lymph node. One of the adjacent lymph nodes contained metastatic endocrine tumour.

The patient's postoperative course was uneventful and subsequent acid studies, serum gastrin and secretin test were normal (*Table 1*, *Figures 2* and *3*). She is completely asymptomatic and off any form of treatment 43 months after the operation.

Case 4. A 35-year-old woman initially presented in June 1984 with a perforated proximal jejunal ulcer. At surgery a 1·5 cm tumour was removed from the posterior wall of the first part of the duodenum; histology revealed a gastrinoma. The perforation was closed and no further definitive surgery performed because of severe peritoneal soiling. Her basal acid output, fasting and stimulated gastrin levels were in keeping with the ZES (*Table I*). CT scan and selective coeliac arteriogram revealed a vague 3·5 cm mass in the head of the pancreas. The basal acid output was inadequately reduced from 58 to 18 mmol/h

Table 1 *Pre-operative and most recent postoperative acid studies and basal and stimulated (secretin) gastrin values*

	Age (years)	Acid output (BAO/MAO) (mmol/h)		Serum gastrin (basal/stimulated) (pmol/l)	
		Pre-operative	Postoperative	Pre-operative	Postoperative
Case 1*	36	37/62	16/29 (53)	198/334	127 (53)
Case 2*	22	50/55	6/24 (59)	236/1099	19/25 (57)
Case 3	16	38/36	6/25 (33)	113/198	27 (33)
Case 4	35	58/75	12/32 (8)	481/583	97/146 (22)
Case 5	38	34/94	0·5/25 (4)	138/207	12 (8)

*Short term results have been reported elsewhere[9,14]

Figures in parentheses are months after operation

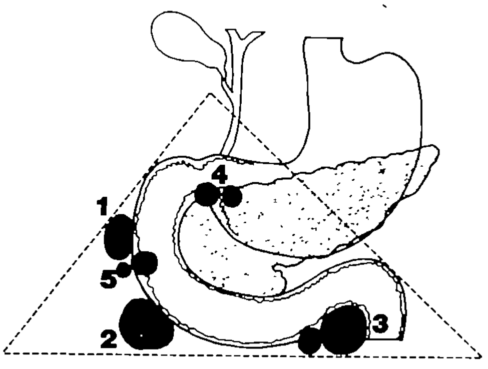

Figure 1 *Location of primary tumour ● and/or lymph node metastases ● in the gastrinoma triangle*[4]*. Numbers refer to site of tumour in the five cases. Adapted from the American Journal of Surgery and reprinted with permission*

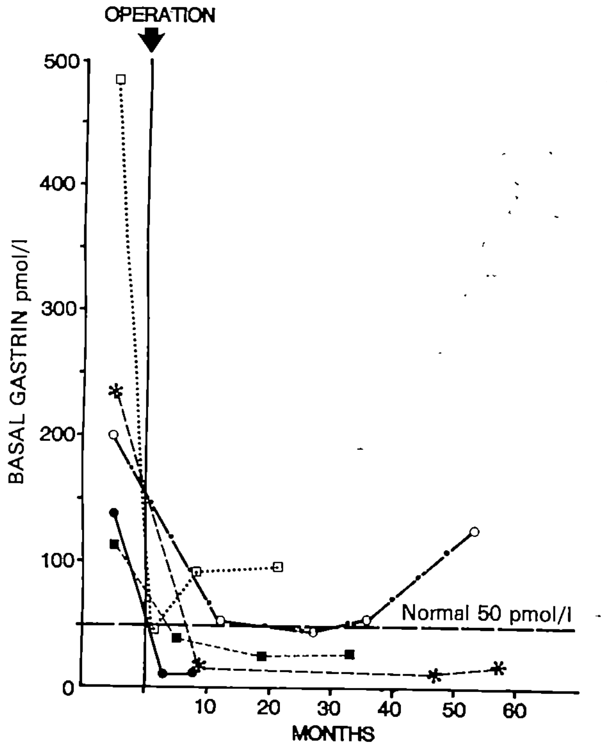

Figure 2 *Pre- and postoperative basal serum gastrin levels during the follow-up period after excision of tumour.* ○, *Case 1;* ∗, *case 2;* ■, *case 3;* □, *case 4;* ●, *case 5*

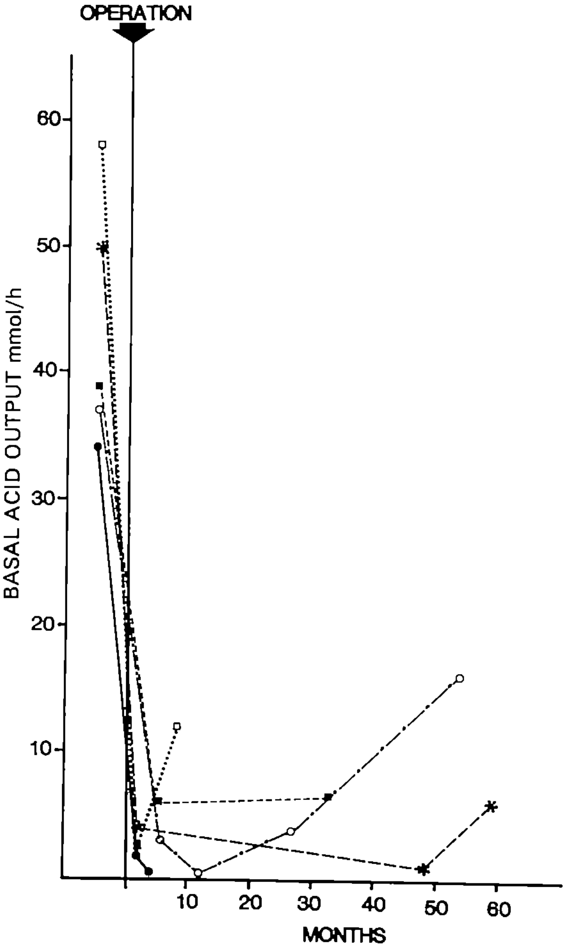

Figure 3 *Pre- and postoperative basal acid output (BAO) during the follow-up period after excision of tumour. Symbols as for* Figure 2

on an oral dose of cimetidine 400 mg. On re-exploration 6 weeks later an incompletely resected duodenal wall tumour and several adjacent lymph nodes were found and removed (*Figure 1*) and a vagotomy and pyloroplasty were added to the procedure.

Histology confirmed the presence of endocrine tumour in the duodenal wall and the lymph nodes adjacent to it contained metastatic tumour.

The patient had an uneventful postoperative course with normal acid and secretin test 3 weeks after surgery. However, repeat tests carried out 8 months after surgery showed basal hypersecretion and a raised serum gastrin level (*Table 1, Figures 2* and *3*). Prophylactic treatment with ranitidine 150 mg b.d. was commenced postoperatively, and she remains well 22 months after surgery.

Case 5. A 38-year-old man presented with a 3 year history of intermittent diarrhoea associated with epigastric pain after meals which responded to an H_2 receptor antagonist. Endoscopy revealed gastritis and extensive duodenitis. The pentagastrin test, serum gastrin and secretin test were in keeping with the ZES (*Table 1*) but imaging techniques (ultrasound, CT scanning, ERCP and angiography) failed to localize a definite tumour. The patient's hypersecretory state was well controlled on ranitidine 150 mg (basal acid output 5·0 mmol/h after 1 h). At surgery a 1 cm tumour was found and excised from the posterior aspect of the second part of the duodenum as well as two enlarged lymph nodes, contiguous to the tumour and embedded on the surface of the pancreas (*Figure 1*).

Histology of the tumour confirmed the diagnosis of a gastrinoma with positive stains for gastrin only. One of the lymph nodes, contiguous to the tumour contained metastatic gastrinoma.

to the tumour, contained metastatic gastrinoma.

Table 2 *Results following removal of presumed primary extra-pancreatic gastrinoma and/or lymph node metastases*

Author	Case no.	Site of primary	Nodal involvement	Gastric surgery	†Serum gastrin (pg/ml) (postoperative)	Follow-up (years)
Wilson[2]	12	n.d.	Yes	Total gastrectomy	50	19
	13	n.d.	Yes	Total gastrectomy	83	19
	14	n.d.	Yes	Total gastrectomy	Normal	15
	19	n.d.	Yes	Total gastrectomy	<100	3
	21	n.d.	Yes	Total gastrectomy	126	7
Wolfe[3]	3	n.d.	Yes	Total gastrectomy	20	1
Stabile[4]	2	n.d.	Yes	Total gastrectomy	48	8
	4	*Head	Yes	Total gastrectomy	46	7
	5	*Head	Yes	—	43	9 months
Friesen[6]	—	n.d.	Yes	Total gastrectomy	83	3
	—	n.d.	Yes	Total gastrectomy	57	18
	—	?Site	Yes	—	Normal	3
	—	?Site	Yes	—	Normal	6
Richardson[7]	1	n.d.	Yes	Vagotomy and pyloroplasty	367	14
Richardson[8]	A	n.d.	Yes	Proximal gastric vagotomy	96	5
	C	?*Site	Yes	Proximal gastric vagotomy	61	3
Harmon[10]	2	n.d.	Yes	Proximal gastric vagotomy and parathyroidectomy	100	1 1/2
	6	n.d.	Yes	—	Normal	1 1/2

*Extrapancreatic; n.d., not detected; †normal value, <100pg/ml

The postoperative course was uneventful and acid secretion at 4 months and gastrin levels 8 months after the operation were normal (*Table 1*, *Figures 2* and *3*).

Methods

Basal and stimulated (pentagastrin 6 μg/kg) gastric acid studies were measured using a method similar to that described from our laboratory[11] and the serum gastrin levels were determined by a CIS radio-immunoassay kit (normal value <50 pmol/l). The secretin test was performed by an intravenous bolus of Secretin (Boots) 2 units/kg body weight over 2 min. Serum samples were taken at −15, 0, 2, 5, 10, 15 and 30 min. A rise in gastrin of >90 pmol/l over basal indicates a positive response[12].

Discussion

The advent of the H_2 receptor antagonists ushered in the new era of conservatism in the management of the ZES[13,14] and this has gained further momentum with the realization of the benign outcome in patients with disease localized to the gastrinoma triangle. The latter, as described by Stabile *et al.*[4], is defined by the junction of the cystic duct and common bile duct superiorly, the junction of the second and third portions of the duodenum inferiorly and the junction of the neck and body of the pancreas medially. Removal of an extra-pancreatic primary and/or lymph node metastases in the triangle has yielded excellent results when combined with total gastrectomy, vagotomy or, indeed, when carried out without additional gastric surgery (*Table 2*).

The results of the present study support the view regarding the relatively bland nature of such tumours and offer evidence in favour of simple surgical excision without concurrent gastric surgery. The immediate postoperative acid studies, serum gastrin and secretin tests returned to normal levels in all five patients, and have remained so in three patients (cases 2, 3 and 5) followed up for periods of 57, 33 and 8 months respectively. In this respect it is of interest that gastrin levels remained normal for a median follow-up of 7 years (range 1–19) in no fewer than 15 or possibly 16 of the 18 previously reported cases (*Table 2*).

The frequent findings of normal gastrin and basal acid secretion levels many years after removal of extra-pancreatic tumours or lymph node metastases point against the need for additional gastric surgical procedures at the time of the initial resection. Total gastrectomy would appear ill-advised in this setting, and the need for vagotomy is open to question. It has been argued that prophylactic vagotomy, by virtue of its inhibition of gastrin stimulated acid secretion[15], may delay the onset of a symptomatic relapse or reduce the dosage of H_2 receptor antagonists to control acid hypersecretion[8] in the relatively small number of patients who develop recurrent disease. Prophylactic vagotomy was in fact carried out in both patients in the present series who on follow-up had hypergastrinaemia and raised basal acid secretion unassociated with clinical relapse. The question of a second look laparotomy in patients with symptomatic or indeed biochemical recurrence needs careful consideration. Removal of a recurrent tumour may grant the patient a further respite and, possibly, reduce the need for continued medical treatment. On the other hand, knowledge of the slow growing nature of the tumour[5] makes it difficult to resist the temptation of controlling acid hypersecretion with an appropriate H_2 receptor antagonist and delaying surgery until such time as control becomes difficult or the presence of an unequivocal tumour becomes apparent on imaging.

It is interesting to note that no primary was detected in two of the patients in the present series (cases 1 and 2) and in 13 of the 18 previously reported cases (*Table 2*) and that gastrin levels returned to normal following removal of the apparent metastatic nodes alone. Removal of such nodes at the time of total gastrectomy in ZES patients with an unidentified primary tumour may help explain the so-called regression phenomenon attributable to the removal of the target organ[16–18]. The origin of these so-called 'solitary metastatic lymph nodes' remains obscure. 'Involution' of the primary tumour has been suggested[5], but Sircus' hypothesis[19] that these may represent an ectopic primary, surrounded by a cuff of lymphocytes and plasma cells and thus mimicking an involved lymph node, is perhaps more attractive. One might speculate further that these tumours, which seem to occur at a much younger age group than the average age reported with the ZES[20], represent remnants of the G cells of the fetal pancreas which normally disappear at the time of birth. While the presence in two of our patients (cases 1 and 2) of tumour in lymphoid tissue, with lymphoid follicles and germinal centres, is strongly suggestive of lymph node metastases, it should be noted that even these features do not exclude an ectopic primary. Lymphoid follicles with germinal centres may be found in situations other than in lymph nodes[21]. The finding of raised gastrin and basal acid secretory levels 53 months after removal of the solitary node in case 1, however, makes it unwise to support Sircus' hypothesis unreservedly.

The results of this study vindicate the policy of routine laparotomy in all cases with the Zollinger–Ellison syndrome unless the patient is unfit for surgery. All macroscopic tumours situated in the duodenal wall, extrapancreatic region and lymph node metastases should be removed. Vagotomy may be considered in the management of patients in whom incomplete removal of the tumour is suspected[22] but total gastrectomy is no longer indicated.

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Re-operation rate for ingrowing toe nail treated by phenolization: 3 year follow-up

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Several operations have been advised for ingrowing toe nails[1,2], but follow-up studies are mostly limited to a few months. We wished to conduct a follow-up study with an interval of at least 3 years after operation to obtain an accurate assessment of recurrence requiring re-operation.

Patients and methods

All patients with ingrowing great toe nail operations performed in 1982 were listed. Those patients with telephones were identified in the 1985 telephone directory. After an interval of at least 3 years from initial treatment the patients were contacted by phone to ascertain whether re-operation had been necessary.

Patient selection and operating technique

All patients presenting with pain and tenderness with or without swelling and redness of the nail border were placed on the next available theatre list (2–3 days).

The technique was similar to Ross's[1] description. This involved antiseptic preparation, ring block and exsanguination by rubber operating glove tourniquet (the cut end of a rubber finger being rolled back towards the big toe base). A dry field was considered important for optimum cautery effect of phenolization. A 2–3 mm lateral nail segment was cut free and removed with artery forceps, taking care to observe nail removal over the basal lateral matrix. Eighty per cent phenol was applied via cotton tip orange stick to the lateral horn germinal matrix for 3 min. Alcohol washes then neutralized the phenol. Longitudinal and circumferential first-aid plaster dressings were applied. This controlled postoperative bleeding on tourniquet removal yet allowed the wearing of normal shoes. Instruction to use the plasters throughout the day but to leave the toe open to the air at night was given.

Results

During 1982, 290 patients were treated for ingrowing toe nails. Sixty-two were found listed in the 1985 telephone directory. Two were unavailable for questioning and we conducted this study on the remaining 60. The distribution of age, sex and which side of the nail was involved are shown in *Table 1*.

Following operation, two nails (2·6 per cent) had a moderately severe inflammatory reaction which settled rapidly with daily dressings and antibiotics. No cases of osteitis were observed.

Seven toes required re-operation. This represents 9·2 per cent of affected toes and 8·1 per cent of nail sides. Six of these had re-operations for further ingrowing nail symptoms: two each at 2, 4 and 12 months. One of the cases at 4 months had a second re-operation at 10 months. The other case was one of three patients who grew nail spicules. Two controlled these by paring and the last, who re-attended at two years, required spicule removal and matrix cauterization.

Discussion

In previous attempts to do follow-up studies on patients with similar minor conditions we encountered great difficulty. Patients who were asymptomatic failed to attend review appointments or to answer postal questionnaires. With a high proportion of 'don't knows' no meaningful conclusions could be drawn. As our aim was to establish the re-operation rate, it was reasonable to expect an unequivocal answer to a telephone enquiry. We knew that patients with telephones were a biased sample. However, we could see no reason why the re-operation rate in this group should be markedly different from the re-operation rate for all patients. Despite the two unavailable patients, we feel the 100 per cent response from the remaining 60 allows one to place confidence in the findings.

We considered the four re-operations occurring in the first 4 months as early (5·2 per cent of toes or 4·7 per cent of nail sides). They may represent inadequately performed initial operations. A common error was failure to notice a small portion of broken-off nail under cover of the nail border continuing to give irritation. Sometimes the width of nail segment removed was insufficient leaving an irritating border rubbing against granulation tissue. The four recurrences (again 5·2 per cent of toes and 4·7 per cent nail sides) at 1 and 2 years and the second recurrence at 10 months we regarded as late and attributed to inadequate matrix destruction. Where re-operation was necessary (even for a third time) we had no hesitation in repeating the original procedure and this has been well accepted by the patients.

In the study by Varma *et al.*[3], 11 per cent of phenol cauterized toe nails required re-operation within a review time of 6 months. Morkane *et al.*[4] had no patients requiring re-operation over an average of 14 months follow-up but had nail spicule formation rate of 7·4 per cent. Our nail spicule rate is just under half of this (3·4 per cent) and certainly less than the 25 per cent noted by Varma *et al.*[3].

Siegle *et al.*[5] claim a zero re-operation rate, although no details are given of their length of follow-up. Two points of technique may have contributed to their figures; they curretted the germinal matrix before phenolization and applied phenol in three separate 30 s periods, rubbing the phenol into the basal matrix.

None of the previous studies have had as long a follow-up period as 3 years. Taking into consideration the constantly changing junior staff who perform most of the operations, our results can be considered as reasonably satisfactory.

It has been our practice to review our patients at 3 and 9 weeks postoperatively. By this time virtually all cases are well healed. The patient is then instructed to return at once should any problems arise. This policy seems to have worked well in practice and our 3 year review does not indicate any need for change.

Table 1 *Distribution of age, sex and laterality in 60 patients*

Median age	21 years
Male:female ratio	63 per cent: 37 per cent
Total toes	76
One toe affected	44 patients (73·3 per cent) 25 right 19 left
Both toes (simultaneously or within 3 months)	16 patients (26·7 per cent)
Affected sides	86
Overall lateral involvement of toe	72 per cent
Overall medial involvement of toe	28 per cent
Both medial and lateral involvement same toe	13 per cent 10 patients

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Role of aspiration biopsy cytology in the diagnosis of cold solitary thyroid nodules

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The solitary thyroid nodule is a common clinical problem. While the reported incidence of malignancy in operated cold nodules ranges from 2 to 28 per cent the corresponding figure for palpable thyroid carcinoma is low, 0·05–0·15 per cent[1]. This discrepancy necessitates a specific diagnosis to avoid unnecessary surgery. Aspiration biopsy cytology has proved to be useful[2,3] and the aim of this report is to assess its value.

Patients and methods

In a prospective study from June 1984 to March 1986 a total of 124 euthyroid patients who had isotope scan proven solitary cold nodules had aspiration biopsy cytology followed by surgery. Ninety-four were females and thirty were males (3:1 ratio). Their ages ranged from 7 to 65 with a median of 35 years. No patient had previous thyroid surgery or head and neck irradiation. Aspiration biopsy cytology was performed by the cytologist and reported as malignant, neoplastic (abundance of follicular cells) or benign. Surgery consisted of total removal of the involved lobe including the isthmus but if cancer was detected the resection was extended to a total or subtotal removal of the contralateral lobe.

Results

The aspirate was reported as benign in 89 patients, malignant in 7 and neoplastic in 28. Histopathology revealed 54 follicular adenomas, 61 colloid goitres, 8 carcinomas and 1 lymphocytic thyroiditis. All seven cytological malignancies were correct (specificity 100 per cent) but in one of eight histopathological malignancies aspiration biopsy cytology was reported as benign (sensitivity 88 per cent). This false negative result was due to a sampling error because early cancer was found in another part of the excised lobe (*Table 1*).

Discussion

One limitation of aspiration biopsy cytology is an error of sampling and this is illustrated by the negative finding in one patient with a benign thyroid cyst in whom malignancy was found in a remote ipsilateral lesion. Occult carcinoma occurs with a frequency range of 5–20 per cent and probably has no clinical significance[4].

Follicular carcinoma is diagnosed histologically by infiltration into the tumour capsule and/or angioinvasion; such criteria are not available to the cytologist, and surgery is therefore recommended for patients with neoplastic aspirates. Although no patient with neoplasia proved to have a malignancy other studies have reported this in up to 50 per cent[5,6]. Aspiration biopsy cytology has resulted in a more restrictive attitude to operation in patients with solitary thyroid lesions, reserving surgery for patients with malignant or neoplastic aspirates. Finally the low incidence of carcinoma (6·5 per cent) may be attributed to the small population of older individuals and the absence of childhood neck irradiation.

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Table 1 *The result of aspiration biopsy cytology compared with permanent histopathology in 124 patients with solitary cold thyroid nodules*

	Aspiration biopsy cytology	Carcinoma	Follicular adenoma	Colloid goitre	Thyroiditis
Malignant	7	7	0	0	0
Neoplastic	28	0	18	10	
Benign	89	1	36	51	1
Total	124	8 (6·5)	54 (43·5)	61 (49)	1 (0·8)

Values in parentheses are percentages

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Infusion cholecystography as the initial investigation in acute biliary disease

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The benefits of early surgical intervention in acute gallbladder disease have been extensively reviewed elsewhere[1–3], yet the decision to subject the patient to surgery is heavily dependent on accurate diagnosis if unnecessary operations are to be avoided.

Although ultrasound has been shown to have a predictive value similar to that of HIDA (diethylacetanilido-iminodiacetic acid) scintigraphy when specific assessments of the thickness of the gallbladder, oedema and perforation of the gallbladder were made[4], interpretation remains subjective[5].

Prolonged infusions of biliary contrast media were first introduced by Lindblad in 1978[6] and the reliability of the method was confirmed subsequently by Norrby *et al.*[7] and Dykes *et al.*[8]. The latter series demonstrated a true positive rate of 88 per cent with infusion cholecystography which was almost identical to that of HIDA scintigraphy (90 per cent) but superior to that of ultrasonography (77 per cent).

Patients and methods

Over an 8 month period 42 consecutive patients presenting with features of acute cholecystitis warranting emergency surgical admission were assessed with ultrasonography and infusion cholecystography within 24 h of admission. In the original protocol it was decided that a positive infusion cholecystogram would constitute the determinant investigation for exploratory surgery.

Ultrasonography of the hepatobiliary apparatus was performed the morning following admission on the fasted patient. Information was obtained regarding the presence of stones in the gallbladder and biliary tree, the thickness of the gallbladder wall, the presence of hepatic parenchymal abnormalities, the state of the pancreas and the state of the surrounding viscera.

Infusion cholecystography was performed by infusing 100 ml meglumine iodoxamate (Endobil) in 1 litre of normal saline on the ward between midnight and 8 a.m. of the morning following admission. Plain radiographs of the right upper quadrant were obtained at the end of the infusion. Tomography was not performed routinely in contrast to the practice in previous studies. This variation in technique was intended in the original protocol to reduce the load imposed by the investigative procedure on the radiology department. Only those patients with no apparent opacification of contrast medium anywhere in the biliary tree were subjected to tomography. Cholecystography was considered positive if stones were demonstrated in the gallbladder or if contrast medium appeared within the duodenum or bile ducts in the absence of opacification of the gallbladder[8]. The presence of a non-functioning gallbladder or the presence of stones in a functioning gallbladder were considered to confirm the clinical impression of acute cholecystitis.

Patients found to have evidence of acute biliary disease underwent early exploration on the next available operating list. Patients with normal infusion cholecystography and ultrasonography were investigated further.

Results

Twenty-six patients (62 per cent) had evidence of biliary disease on infusion cholecystography. The common bile duct was clearly visualized with calculi within it in two cases. The gallbladder was functioning in 6 and non-functioning in 20 patients. In another two patients (4·8 per cent) the contrast medium failed to concentrate sufficiently to allow visualization of the biliary tree. Liver function tests were entirely normal in these cases. Cholecystography was negative in 14 (33 per cent) patients. In none of the patients were there any adverse reactions to the infusion of the contrast medium.

Ultrasonography revealed evidence of biliary disease in 23 (54·7 per cent). Stones were seen in all cases. The gallbladder wall was thickened in 12 and the gallbladder grossly distended in 8 patients. The common bile duct was dilated in three but in a further five it could not be adequately visualized because of excess bowel gas. In another two patients the entire biliary apparatus could not be satisfactorily identified. In one patient multiple hepatic metastases were present without evidence of other pathology and in another the right kidney was found to be hydronephrotic. Ultrasonography was reported as normal in 17 (40·4 per cent). In these patients no abnormality was detected in the biliary tree, liver, pancreas and kidneys.

Only one 93-year-old woman with positive infusion cholecystography and ultrasonography was treated conservatively. Twenty-five patients with positive infusion cholecystography underwent surgical exploration on the next available list (mean 72 h, range 2–5 days after admission). In one patient the cause of the acute pathology was found to be a localized perforation of a duodenal ulcer, although the presence of gallstones was indeed confirmed. Four gallbladders were perforated (16 per cent), eight (32 per cent) had developed into empyemeas and two (8 per cent) had developed into mucoceles. Uncomplicated cholecystitis was present in nine patients (36 per cent). In one case (4 per cent) the gallbladder contained several stones but was not acutely inflamed. Stones in the common bile duct were present in four cases (16 per cent).

There were no false positive or false negative infusion cholecystograms. Ultrasound was reported negative in three cases that were subsequently proved positive on infusion cholecystography and at operation. Neither ultrasound nor infusion cholecystography produced false positive results.

The final diagnoses of the 16 patients with negative biliary investigations are shown in *Table 1*. These patients were investigated with intravenous urography, upper gastrointestinal endoscopy and laparoscopy. Four patients had perihepatitis in association with pelvic inflammatory disease (Curtis–Fitz-Hugh syndrome) (10 per cent). The two patients with an unsatisfactory infusion cholecystogram and the two patients with unsatisfactory ultrasonography are indicated in *Table 1*. A definite diagnosis failed to be reached in five patients (12 per cent) despite biliary, urological and endoscopic evaluation.

Discussion

With a large number of patients presenting with suspected acute cholecystitis to our unit but with no nuclear medicine department on site, we decided to adopt infusion cholecystography as the primary and determinant investigation for a consecutive series of 42 patients. We used meglumine

Table 1 *Final diagnoses in patients with negative biliary investigations*

Curtis–Fitz-Hugh syndrome	4
Appendicitis	2 (1)*
Peptic ulceration	
Localized perforation	1†
Acute ulcer	1
Alcoholic pancreatitis	1
Multiple hepatic metastases	1*
Right ureteric colic	1
Uncertain	5 (1)†

* Unsatisfactory infusion cholecystography, † unsatisfactory ultrasound

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iodoxamate (Endobil) in preference to meglumine ioglycamate because in the experience of our radiology department the risk of a reaction was lower with the former preparation. Tomography was used restrictively as we intended to identify a diagnostic procedure that would improve diagnostic accuracy without increasing the burden on the radiology department. The infusion was set up on the ward on the night of admission and a reliable indication as to the need for surgery was available the following morning. The decision to operate was made if the cholecystographic findings confirmed the clinical diagnosis of acute cholecystitis as in no case was ultrasound positive and cholecystography negative. Excluding the single patient with positive infusion cholecystography and ultrasonography who was treated conservatively because of her advanced age, all the other cases with a positive infusion cholecystography were confirmed at operation. In one of the two patients without concentration of the contrast medium it was noted that only half the infusion had been administered at the time the radiography was performed. None of the patients reacted adversely to the infusion and, besides the relative ease of interpretation of the X-rays, in two cases with a dilated common bile duct, the cause was immediately apparent. Ultrasound was useful in determining the size of the gallbladder, the thickness of its wall and in identifying alternative pathology.

This study confirms the usefulness and reliability of infusion cholecystography in acute biliary disease, which if employed in conjunction with ultrasonography can achieve a diagnostic rate similar to that afforded by isotope scanning. Furthermore the method is cheap, easy to perform on the ward, does not involve skilled interpretation and provides an immediate objective result. These features are of particular interest to surgeons intending to operate early in acute cholecystitis, perhaps even if isotope scanning services are readily available.

Acknowledgements

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Recurrent pancreatitis contributing to choledochal cyst formation

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We report three cases of choledochal cyst. The calibre of the common bile duct in each of them was demonstrated by ultrasonogram, CT scan, radiography and laparotomy to be almost normal before recurrent attacks of pancreatitis, following which the common bile duct was shown to become grossly dilated. This observation leads us to surmise that recurrent pancreatitis contributes to the formation of choledochal cysts.

Keywords: Choledochal cyst, pancreatitis

It is well known that choledochal cysts can present as acute pancreatitis. Pancreatitis is customarily regarded as a complication or an associated feature of choledochal cyst. So far, no one has pointed out and verified that pancreatitis contributes to the development of biliary cysts. Recently, we had the rare opportunity of observing, on three occasions, rapid dilatation of the common bile duct (CBD), occurring shortly after episodes of proven pancreatic inflammation. The temporal relationship between the two events speaks for a causal role for recurrent pancreatitis.

Case reports

Case 1

A girl aged 4 years and 4 months was admitted with a second attack of epigastric pain and fever, but without jaundice. The serum amylase was 2800 units/l. In view of the marked abdominal tenderness and guarding, she was explored surgically and severe haemorrhagic pancreatitis was found. Calcified nodules were seen all over the omentum. No dilatation of the CBD was detected (*Figure 1A*). A drain was placed, but progress was unsatisfactory because of persistent epigastric discomfort and a serum amylase level >4569 units/l (normal range 56–110 units/l). She was re-admitted 3 months later with increasing pain, jaundice and fever. Ultrasonogram and CT scan demonstrated a choledochal cyst of 6 cm diameter below the liver. Re-exploration confirmed the above finding (*Figure 1B*). Operative cholangiogram failed to visualize the lower end of the CBD. The cyst was excised, followed by hepaticojejunostomy in a Roux-en-Y fashion. The terminal CBD was atretic and was not stitched. The amylase level of the cystic content was >4569 units/l. Histological examination of the cyst wall showed widespread ulceration of the mucosa and marked thickening by fibrous connective tissue. Convalescence was uneventful.

Case 2

A $4\frac{1}{2}$-year-old girl was referred for evaluation of persistent obstructive jaundice. The only significant finding was a liver palpable 3 cm below the right costal margin. A CT scan on admission showed dilatation of the CBD to a maximum of 0·9 cm (*Figure 2*). The serum bilirubin and alkaline phosphatase were 180 μmol/l and 700 units/l respectively. The serume amylase was checked almost daily and the level fluctuated between 100 and 4659 units/l for over 3 weeks. Because of unremitting pain and hyperamylasaemia, an exploratory laparotomy was performed after 6 weeks. At operation, the pancreas appeared oedematous with areas of fat necrosis. The CBD was dilated in a fusiform fashion to 3 cm diameter, while the intrahepatic ducts were similarly dilated. As the operative cholangiogram was unsatisfactory, after removal of the cyst the distal duct was oversewn around a catheter for later radiographic studies. Postoperatively, the amylase level fell rapidly and the jaundice faded. The catheter inserted into the distal CBD stump drained out 50–100 ml clear fluid every day. The fluid looked like pancreatitic juice and was proved to be so by an extremely high level of amylase. Contrast injected down the catheter revealed incomplete pancreas divisum. The lower end of the bile duct joined the duct of Wirsung at an acute angle proximal to a dilated common channel that was 2·2 cm long. There was a low grade stenosis of the common bile duct at its entrance into the common channel (*Figure 3*).

Case 3

A 30-year-old woman was well until age 25 when she required several admissions to hospital for upper abdominal pain. On a recent admission during a severe attack, the serum amylase was >4569 units/l, bilirubin 82 μmol/l and alkaline phosphatase 179 units/l. An ultrasonogram taken 1 year previously had shown a common bile duct of 0·8 cm in diameter (normal <0·6 cm), while an intravenous cholangiogram 4 years previously had shown a normal-sized common bile duct (*Figure 4A*). She improved on a conservative regimen, but subsequently had several similar attacks, all of which were associated with hyperamylasaemia. An intravenous cholangiogram 2 months later showed gross dilatation of the CBD. At operation, a type I choledochal cyst of 8 cm in diameter was found (*Figure 4B*). The lower end of the CBD was markedly narrowed and the pancreas felt indurated and nodular. The choledochal bile showed an amylase level >5685 units/l. Following cystectomy, a Roux-en-Y hepaticojejunostomy was performed. Postoperatively, she did well. Histologically, the cyst wall was almost completely denuded of mucosa and consisted mainly of fibrous tissue with a few muscle fibres interspersed.

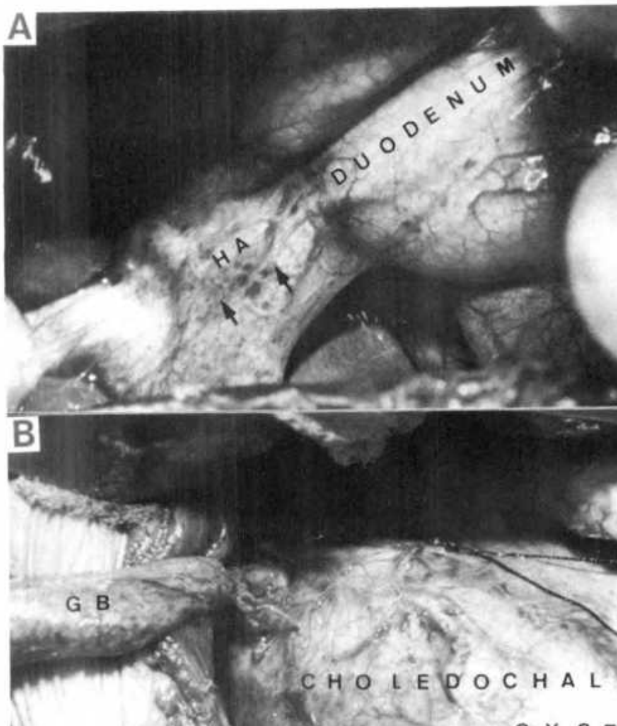

Figure 1 *A, Arrows outline a normal common bile duct beneath the hepatic artery (HA) as seen at the first laparotomy in case 1. B, A large choledochal cyst was found during the second operation. GB indicates gallbladder*

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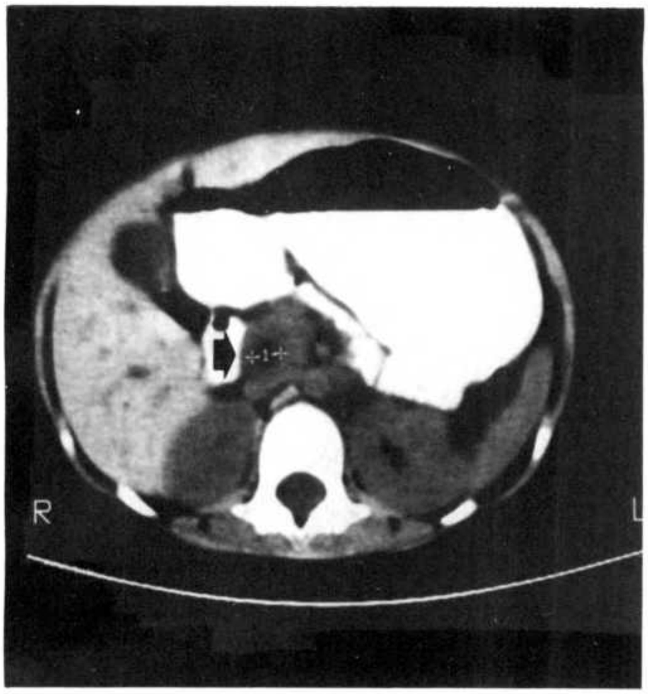

Figure 2 *CT scan of case 2, five weeks before laparotomy, showing slight dilatation of the CBD (arrow) to 0·9 cm*

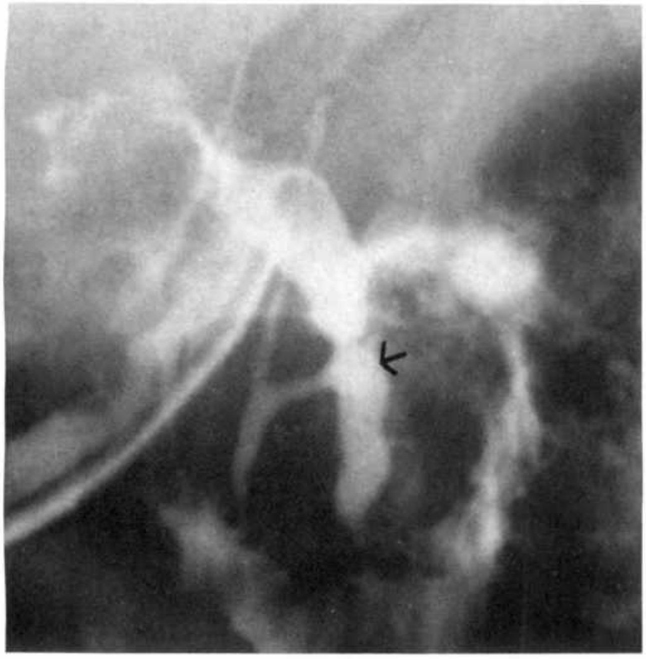

Figure 3 *Cholangiopancreatogram of case 2. The duct of Wirsung joins the choledocus at an acute angle (arrow) 2·2 cm from the duodenal papilla. A low grade stenosis was noted just proximal to the junction. The accessory duct is patent and drains separately to the duodenum*

Discussion

Based on the information to date, it appears that choledochal cysts and pancreatitis are two manifestations of an underlying anomalous arrangement of the pancreaticobiliary ductal system. An elongated common channel allows free reflux of pancreatic juice up the biliary tree and, under certain conditions, bile may find its way to the pancreas[1]. However, despite frequent descriptions of the intimate relationship between the two conditions, no mention has ever been made of a possible role of pancreatic inflammation in the pathogenesis of choledochal cyst, simply because in the majority of case reports the calibre of the CBD was not known before the attacks of pancreatitis leading to the eventual diagnosis of choledochal cyst. In our three patients, the diameter of the CBD was documented to be normal or slightly dilated by ultrasonogram, CT scan, cholangiogram or laparotomy before or at the beginning of bouts of pancreatitis. It was only after weeks or months of persistent or repeated pancreatic inflammation that the CBD became grossly dilated. An extensive review of the literature revealed four similar cases[2-5]. It is a pity that the authors apparently took no notice of the significance of the aforementioned sequence of events, and that the biliary tree anatomy before the attacks of pancreatitis can only be inferred from the description of previous laparotomy findings in every instance (*Table 1*). None the less, the case records lend support to our contention, as do the following observations. All our three patients, who were previously not jaundiced, developed obstructive jaundice during attacks of pancreatitis. In all these cases, the distal choledochus surrounded by indurated and oedematous pancreatic tissue appeared markedly narrowed. It is conceivable that the bile duct can readily be compromised by acute or chronic inflammatory changes. The fact that some cases of choledochal cyst present late in life favours an acquired aetiology in this group of patients. Most patients with choledochal cyst presenting after 1 year of life have recurrent episodes of abdominal pain, many of which were characterized by hyperamylasaemia[6].

At present, the most plausible explanation for the development of choledochal cyst is the combined effect of weakness of the bile duct wall and an increase in intraluminal pressure secondary to a stenosis at the distal choledochus. The role of outflow obstruction was stressed recently[7]. Experimental studies showed that pancreatic juice flowing into the CBD which was not obstructed failed to produce such cystic dilatation as was usually observed in children[1]. Whether the distal stenosis is congenital or acquired remains undetermined. We believe that recurrent pancreatic inflammation, either by compressing and obstructing the lower end of the CBD or by aggravating a pre-existing stricture, can be an important precipitating factor in the pathogenesis of choledochal cysts in selected patients during a certain stage of cyst development. This mechanism, like all the twenty-odd others proposed thus far, cannot be applied to all cases of choledochal cyst which is nowadays regarded as a conglomerate of a spectrum of lesions[8], so much so that one can argue: choledochal cysts can enlarge in the absence of pancreatitis; not all patients with cysts have common channel anomalies of the CBD and recurrent pancreatitis in association with common channels can cause bile duct stenosis without cystic dilatation[8].

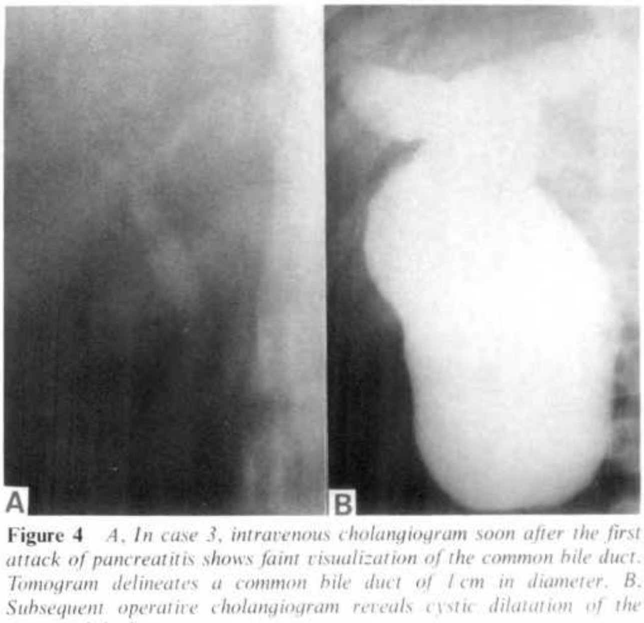

Figure 4 *A. In case 3, intravenous cholangiogram soon after the first attack of pancreatitis shows faint visualization of the common bile duct. Tomogram delineates a common bile duct of 1 cm in diameter. B. Subsequent operative cholangiogram reveals cystic dilatation of the common bile duct*

Table 1 *Analysis of the four reported cases of choledochal cyst (CC) developing after recurrent attacks of pancreatitis with prior laparotomy-proven normal common bile duct (CBD)*

	Tsardakas 1956	Blumenstock 1957	Cuschieri 1959	Agrawal 1979
Sex/age (years)	F/34	F/4½	F/27	M/56
Documentation of CBD status	During laparotomy for suppurative pancreatitis showing normal CBD	During laparotomy for perforation; normal CBD found	During laparotomy for pancreatitis showing normal CBD	Twice during laparotomy for pancreatitis showing normal CBD
Duration between documentation of CBD status and diagnosis of CC	2 months	4 years	5 years	13 years and 1 year
Event between documentation of CBD status and diagnosis of CC	Recurrent pancreatitis	Six attacks of abdominal pain believed to be pancreatitis	Five episodes of abdominal pain with hyperamylasaemia	Recurrent pancreatitis
Cyst morphology				
Type	I	—	I	I
Size	6 cm in diameter	2·5 cm diameter	Containing 700 ml bile	12 cm diameter

While distal bile duct obstruction is common in patients with choledochal cyst, weakening of the duct wall is just as important. In our three patients, histology of the excised cyst wall showed degenerative changes, which can be attributed to the deleterious effect of extremely high concentrations of amylase in the cyst content, present in all these cases.

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Endoscopic management of common duct stones without cholecystectomy

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Endoscopic sphincterotomy was attempted in 81 patients with gallbladders for the primary management of symptomatic common duct stones and was successful in 80. Immediate complications occurred in six (7 per cent) and one patient died (1 per cent). Clearance of the common duct was achieved in 70 (86 per cent). Eight patients required surgery for failed clearance of the duct and suffered no operative mortality. Of 70 patients with cleared ducts, 5 underwent elective cholecystectomy. Four other patients with persistent or recurrent symptoms have required cholecystectomy, also without mortality. Sixty-one patients were reviewed 12–44 months (mean 24; median 22 months) after endoscopic sphincterotomy. Eighteen have died, none from biliary disease. Forty-three patients remain alive and well, free of biliary symptoms since endoscopic sphincterotomy. When the surgical risk of cholecystectomy and choledocholithotomy is high, endoscopic sphincterotomy is effective and safe. Routine cholecystectomy is not indicated when the common duct has been cleared.

Keywords: Common bile duct, endoscopic sphincterotomy

Endoscopic sphincterotomy for the treatment of complications related to common duct stones is steadily becoming more widely available and accepted. This is not only so in those patients who have previously undergone cholecystectomy but also in patients with intact gallbladders[1–3]. This paper reports the short- and medium-term results of endoscopic treatment of common duct stones in a group at high risk from surgery.

Patients and methods

Between July 1981 and December 1984, 81 consecutive patients (31 men and 50 women) with intact gallbladders were seen with symptoms related to the presence of common duct stones. Fifty-six (69 per cent) were specifically referred for endoscopic management from other hospitals in the North West of England and North Wales. Their ages ranged from 28 to 94 with a mean of 76 years (median age 79 years). All but seven were aged over 60 and 41 were over 80. In the seven patients under 60, six presented with obstructive jaundice and one 28-year-old woman was referred with a retained common duct stone after a difficult cholecystostomy for empyema of the gallbladder.

The main presenting symptoms in the 81 patients were jaundice in 44, cholangitis in 15, acute pancreatitis in 5 and pain in 17. Many patients presented with a combination of symptoms. Other conditions were present in 32 patients, most commonly previous myocardial infarct or stroke (17), treated malignant disease (6) and diabetes mellitus (5). Except where antibiotic treatment had already been instituted for the treatment of cholangitis, all patients received mezlocillin 2g IV before endoscopic retrograde cholangiopancreatography (ERCP). Antibiotic treatment was continued where indicated on an individual basis. Patients were sedated with intravenous diazepam and pentazocine. Hyoscine-*n*-butylbromide (Buscopan) or glucagon were given intravenously for duodenal relaxation.

ERCP was performed using Olympus JF1T or JF1T10 duodenoscopes. Attempts were made to avoid overfilling of the biliary system on cholangiography and no specific attempt was made to opacify the gallbladder. Endoscopic sphincterotomy was performed using either a Classen–Demling sphincterotome or a fistulotomy knife with an Erbotom diathermy unit. Stones were extracted using baskets or balloon catheters where possible and attempts were made to fragment and extract large stones. Where stone extraction was unsuccessful a pernasal catheter was inserted and the duct perfused with 2 litres of 5 per cent dextrose daily for up to one week, interim pernasal cholangiography being used to assess passage of stones. Where perfusion failed to achieve clearance of the duct, repeat attempts at endoscopic extraction were performed after one week.

Follow-up

Contact was made with the patients, their relatives or their general practitioners in order to establish their current state of health. When patients had died, the cause of death was established, either from records of the Registrar of Births, Marriages and Deaths or from the Family Practitioner Committee.

Results

ERCP findings

Dilated bile ducts were present in 69 of 81 patients. Most patients had a single common duct stone approximately 1 cm in diameter. The gallbladder filled at ERCP in 40 of 81 patients, although no particular attempt was made to obtain filling. Stones in the gallbladder were demonstrated in 53 of 81 patients, either by ERCP or by ultrasound. Endoscopic sphincterotomy was achieved in 80 of 81 patients (99 per cent).

Complications

Complications of endoscopic sphincterotomy occurred in six patients. Haemorrhage requiring treatment occurred in four patients immediately after endoscopic sphincterotomy. Two of these required transfusion only and recovered. The other two required operation for bleeding; one had the bleeding point oversewn, the common duct having been cleared of stones endoscopically. The second patient, an 85-year-old woman with obstructive jaundice, underwent surgery for bleeding 48 h after endoscopic sphincterotomy, initially made a good recovery and was transferred back to her referring unit. She developed further bleeding one week later and her physician considered that further surgery was not warranted. She subsequently died. One patient had retroperitoneal perforation evident radiologically, but not clinically; another patient developed acute pancreatitis. Both recovered with conservative treatment.

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Common duct clearance

Clearance of the duct had not been attempted in the patient who died from haemorrhage. The common duct was cleared of stones in 70 of the remaining 80 patients. Pernasal catheters were used in 17 patients, but in only 3 did cholangiography during the following week demonstrate a clear duct. In eight patients the catheter 'fell out'. Common duct clearance failed in ten where the stones were too large to be extracted or passed spontaneously and fragmentation was unsuccessful. All ten were over 80 years of age. Seven underwent cholecystectomy and choledocholithotomy during the same admission without mortality. One further patient developed recurrent obstructive jaundice 4 months after endoscopic sphincterotomy and underwent cholecystectomy and choledocholithotomy. Two patients did not undergo operation and one died of left ventricular failure 6 months after endoscopic sphincterotomy without recurrence of biliary symptoms. The second patient is alive and well after 18 months with no clinical evidence of biliary disease.

Surgery

Of 70 patients whose ducts were cleared after endoscopic sphincterotomy five underwent elective cholecystectomy performed by their referring surgeons after the acute phase of their illness had settled. In only one of these was exploration of the common duct necessary, one stone being removed from a duct that was clear after endoscopic sphincterotomy. This patient had gallbladder stones. Cholecystectomy for persisting or recurrent symptoms was necessary in four patients <6 months after endoscopic sphincterotomy. Exploration of the common duct was unnecessary. In one of these patients the gallbladder had been shown to be free of stones at ERCP and in three of the four the gallbladder had filled.

Follow-up

Sixty-one patients with cleared common ducts who did not undergo surgery were reviewed between 12 and 44 months after endoscopic sphincterotomy (mean 24; median 22 months).

Eighteen patients died during the review period. All were elderly (mean 78; median 80 years), except one 47-year-old woman with cirrhosis caused by chronic active hepatitis who died of liver failure. No deaths occurred because of biliary disease and none of the patients had suffered symptoms related to the gallbladder. Forty-three patients with cleared ducts remain alive and well after endoscopic sphincterotomy. Although nine patients report dyspeptic symptoms most commonly treated with antacids or H_2-receptor antagonists, none has required treatment for recurrent biliary symptoms.

Discussion

Despite the large volume of information available regarding the risks of biliary surgery, the morbidity and, in particular, the mortality associated with cholecystectomy and exploration of the common duct are difficult to define. Although elective biliary surgery, including exploration and removal of stones from the common duct is safe in young, fit patients[4,5], morbidity and mortality steadily increase with the addition of each of a number of interlinked risk factors[6]. These factors include increasing age[4,5,7,8], with the attendant risk of cardiovascular and renal disease; jaundice[4,9]; cholangitis[10,11]; pre-existing anaemia[4] and the extent of the necessary surgery[8,12,13]. In the patient with jaundice[14] or cholangitis[10], surgery for benign causes is less hazardous than for malignant disease. However, even in patients undergoing cholecystectomy and common duct exploration for gallstones, postoperative mortality can be 20 per cent[12] or higher[6] when two or more risk factors are present.

Exploration does not always conclude in successful clearance of the duct. Residual stones can be expected in approximately 5 per cent of patients[15], but again, the risk of this is related to a number of factors, particularly to the technique of exploration[12,13] and the availability of operative cholangiography[16] and choledochoscopy[17]. Although the morbidity of extraction of residual stones using the T tube track is minimal[18], this method is not always appropriate and patients may then be exposed to further morbidity and mortality from reoperation. Endoscopic sphincterotomy for common bile duct stones is achieved in up to 98 per cent[19] of patients in whom it is attempted and the duct can be cleared in about 90 per cent[20]. In this series, sphincterotomy was achieved in 80 out of 81 patients (99 per cent), although clearance of the common duct was possible in only 86 per cent.

The immediate complications of endoscopic sphincterotomy (bleeding, cholangitis, pancreatitis and retroperitoneal perforation) occur in 7–10 per cent of patients with a mortality of between 1 and 2 per cent[1,2,19–21]. It is important to recognize that in most large series patients have been referred for endoscopic sphincterotomy by surgeons who have considered them unsuitable for operation[19,20]. Therefore the complications and mortality of endoscopic sphincterotomy must be interpreted in this light.

In this series, 69 per cent of the patients were referred specifically for endoscopic treatment with the opinion that this was likely to be less hazardous than operation. Our figures of 7 per cent complications with one death (1 per cent) are in keeping with the figures published from other series[1,2,19,21] and are a testament to the safety of endoscopic sphincterotomy, which does not appear to be more difficult or more hazardous in patients with a gallbladder[21–24] than in those without[1,2,19]. Both Cotton[3] and Neoptolemos *et al.*[22] reported the occasional development of acute cholecystitis following endoscopic sphincterotomy. In this series we routinely gave all patients antibiotic premedication and, perhaps as a consequence of this, we have not yet encountered this complication. In a number of European series[3,21–24] of patients treated endoscopically for common duct stones, the need for cholecystectomy for continuing or new symptoms has occurred in less than 10 per cent, most of the operations occurring within the first year. As in the present series, the length of follow-up of these patients is, as yet, limited. However, it is clear that routine cholecystectomy is unnecessary and, because of the selected nature of these patients, many will die from other causes without recurrence of biliary symptoms.

Questions remain. First, for patients in whom common duct clearance is unsuccessful, in common with Leese *et al.*[19], we have found that the acute condition leading to treatment subsides after successful endoscopic sphincterotomy, despite inability to remove stones. It may be that surgical removal of the common duct stones is then safer and, at present, this seems to be the treatment of choice. Because of the fear of cholangitis and obstruction there is a natural disinclination to leave stones in the common duct and, while perfusion and dissolution therapy are unreliable[25,26] and the insertion of endoprostheses can only be regarded as a temporary procedure, elective surgery must be the preferred treatment.

Secondly, are there risk factors which can predict the future development of acute gallbladder symptoms and the need for cholecystectomy in patients with cleared ducts? Solhaug *et al.*[23] and Cotton[20] have proposed that lack of filling of the gallbladder at ERCP may be such a risk factor. This has not been borne out by our experience where three of four patients who required cholecystectomy showed gallbladder filling. Even the absence of stones from the gallbladder does not exclude the need for surgery in the future. One of our patients had resolution of his upper abdominal symptoms following cholecystecomy some months after endoscopic duct clearance, although ultrasound and ERCP had shown no stones in his gallbladder before endoscopic sphincterotomy and his gallbladder was empty at surgery. We have not been able to correlate any clinical, endoscopic or radiological variable with the need for surgery.

There are reports of the non-operative percutaneous management of gallbladder stones, either by percutaneous extraction[27] or by percutaneous instillation of dissolving agents[28]. The successes and complications of these techniques have yet to be analysed, but it may be that they will have some use in the management of selected patients with gallbladder stones after the endoscopic clearance of the common duct.

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Carcinoma of the head of the pancreas: bypass surgery in unresectable disease

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One hundred patients who underwent bypass surgery for unresectable, histologically proven carcinoma of the head of the pancreas were studied to determine: (1) the incidence of a second operation for duodenal obstruction in survivors who had a biliary diversion only; (2) whether the addition of a prophylactic gastroenterostomy is associated with increased mortality. Eighty-six patients (Group A) had a biliary diversion alone while fourteen (Group B) had a biliary diversion and a prophylactic gastroenterostomy. Both groups were comparable regarding sex, age, symptomatology and clinical findings. The postoperative mortality was similar for both groups (Group A, 27·9 per cent; Group B, 14·3 per cent). The mean surgically related hospital stay was 22 ± 6·5 days (Group A) and 20 ± 7 days (Group B). Of the 62 patients in Group A who left hospital, 8 (13 per cent) required a second operation for duodenal obstruction (mean interval 5·4 ± 2·7 months). The in-hospital stay for the second operation was 14·4 ± 7·7 days. The overall survival for both groups was identical at 6 months (35·5 versus *33·3 per cent) and 12 months (19·3* versus *16·7 per cent). This study suggests that prophylactic gastroenterostomy adds no risk to patients requiring biliary diversion for carcinoma of the head of the pancreas. Its routine use is therefore justified since 13 per cent of the patients who survived the biliary diversion required further surgery for duodenal obstruction before death.*

Keywords: Carcinoma of pancreas, gastrojejunostomy, biliary diversion

The incidence of carcinoma of the head of the pancreas is on the increase[1] and it now represents 10 per cent of all the neoplasms of the gastrointestinal tract[2]. Early pancreatic cancer is difficult to diagnose since it may be asymptomatic. It has been estimated that this delay results in 90 per cent of patients with this condition having incurable disease at the time of presentation[3]. In these patients, palliation is the only option open to the surgeon.

Patients presenting with jaundice as their main complaint usually undergo biliary diversion. In patients who also have features of duodenal obstruction a gastroenterostomy is performed simultaneously. Duodenal obstruction alone, however, is an unusual presentation of pancreatic carcinoma and occurs in less than 5 per cent of patients at the time of initial diagnosis[4,5]. Thereafter the incidence of duodenal obstruction increases with time although most patients will die before it becomes clinically relevant[6].

We have retrospectively analysed our results for carcinoma of the head of the pancreas over a 10 year period. The purpose of the review was to determine the incidence of a subsequent operation for duodenal obstruction in survivors who had an initial biliary diversion only. In addition, an attempt was made to assess whether a prophylactic gastroenterostomy confers any increased morbidity and/or mortality.

Patients and methods

A retrospective study was conducted of 100 patients having palliative bypass surgery for carcinoma of the head of the pancreas. These were treated by a group of surgeons at a teaching hospital complex in Glasgow over a 10 year period (1974–83 inclusive).

All patients selected for this study satisfied the following criteria:

1. They had a diagnosis of carcinoma of the head of the pancreas proven histologically either by biopsy at laparotomy or subsequently at post mortem.
2. At their initial laparotomy they had unresectable disease.
3. They underwent bypass surgery at their initial laparotomy.
4. They had no clinical, radiological or laparotomy evidence of duodenal obstruction at their initial presentation.

Six surgeons were involved in the treatment of these patients. One surgeon routinely performed a prophylactic gastroenterostomy. The other clinicians only employed a gastroenterostomy when duodenal obstruction was in evidence and these cases were not included in this study. The prophylactic gastroenterostomy was of the antecolic type and the anastomosis was performed at the most dependent part of the stomach within the antrum. The biliary bypass took the form of a cholecystjejunostomy in all cases.

The patients studied in this report represent 34 per cent of the total number (296) of patients operated upon at the above hospital complex with a diagnosis of pancreatic carcinoma. (A total of 345 patients were recorded as having pancreatic carcinoma but in 49 patients no operative intervention was carried out and therefore the diagnosis remains purely speculative.) Forty-two per cent had carcinoma of the body or tail. In 57 patients (19 per cent) with presumed carcinoma of the head of the pancreas histological proof was not available and fourteen patients (4·7 per cent) had evidence of duodenal obstruction at presentation.

Results

There were 64 men and 36 women with an age range of 45–92 years (mean 65 years). Two groups of patients emerge as a result of surgical treatment. The first group of patients (Group A, $n = 86$) underwent biliary diversion only. The remaining 14 patients (Group B) had a prophylactic gastroenterostomy performed in addition to biliary diversion. The symptomatology of these two groups is illustrated in *Table 1* which shows that no significant differences emerged.

Postoperative progress was then assessed. The mean hospital mortality (i.e. deaths occurring within 30 days of surgery) was 26 per cent (Group A, 27·7 per cent; Group B, 14·3 per cent). The in-patient hospital stay was again similar with 22 ± 6·5 days for Group A and 20 ± 7 days for Group B. Their postdischarge survival was comparable both at 6 months (35·5 *versus*

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33·3 per cent) and 12 months (19·3 *versus* 16·7 per cent). No evidence was obtained to suggest that the patients undergoing a double bypass fared worse than those subjected to a biliary bypass alone and in particular no complications relating to the gastroenterostomy itself (bile reflux, ulceration) were recorded. All patients were dead within 19 months of initial palliative surgery.

Table 1 *Symptomatology*

	Group A ($n=86$)	Group B ($n=14$)
Duration of symptoms before hospital admission (months)	5·0±6·75	5·6±6·1
Percentage of patients with symptoms >3 months	35	43
Symptoms		
Nausea, vomiting*	7%	14%
Upper abdominal pain	21%	14%
Jaundice	56%	57%
Signs		
Hepatomegaly	58%	50%
Pancreatic mass	47%	53%
Wasting	37%	29%
Anaemia	26%	29%
Ascites	5%	0%

*No evidence of duodenal obstruction noted on hypotonic duodenography

Histologically all tumours were adenocarcinomas with 78 per cent (A: 76·7 per cent; B: 78·6 per cent) being poorly differentiated and 22 per cent (A: 22·1 per cent; B: 21·4 per cent) moderately well differentiated tumours.

Of the 62 patients in Group A who survived the procedure of biliary diversion alone, 54 required no further surgery before death. Eight patients (13 per cent) in this group later developed symptoms of duodenal obstruction necessitating a gastroenterostomy. This resulted in complete relief of symptoms in seven patients and partial relief (intermittent vomiting) in one patient. The mean duration between the initial biliary diversion and subsequent gastroenterostomy was 5·4 months. No postoperative deaths were recorded following the second operation but the mean survival after the second operation was only 2·5 months.

Discussion

The diversity of opinion expressed in the surgical literature makes certain aspects of the management of pancreatic carcinoma confusing. Surgeons have long debated the use of prophylactic gastroenterostomy in patients with carcinoma of the head of the pancreas undergoing laparotomy for biliary diversion. No unequivocal answer has, as yet, emerged.

The reported usage of gastroenterostomy in patients with carcinoma of the pancreatic head has varied between 8 and 50 per cent[7,8]. The reason for this wide reported range stems from authors failing to define whether the gastroenterostomy was being performed on a truly prophylactic basis. Consequently a miscellany of problems have been included for analysis. Closer examination of the literature reveals that the need for a subsequent gastroenterostomy to treat developing duodenal obstruction lies between 10 and 20 per cent in most series[6,7,9,10] and 13 per cent in this series. This implies that the routine use of a gastroenterostomy as the initial palliative procedure will be unnecessary in at least 80 per cent of patients and can therefore only be justified if its benefits to the minority outweigh the risks to the majority. The results of this study of two groups of patients with comparable unresectable carcinoma of the head of the pancreas failed to show a disadvantage related to prophylactic gastroenterostomy and support the routine use of this procedure in palliation of this condition.

Patients with pancreatic carcinoma, particularly if jaundiced, tend to have a high morbidity and mortality following palliative surgery. In our series, the mortality for palliative surgery was 26 per cent and was not influenced by the addition of a gastroenterostomy. The main causes of death were bronchopulmonary (14 patients), cardiac (4), renal (5) and pulmonary thrombo-embolism (3). These findings are in keeping with previously recorded series[7,11,12]. Hospital stay, as an expression of morbidity, was not significantly altered by the addition of a gastroenterostomy. However, in the group of patients with biliary diversion only, who required a second operation for duodenal obstruction, the overall hospital stay rose from 22 to 34·5 days, an important increase when one considers the short life expectancy of this group. Postoperative survival was similar in groups A and B and no difference in postsurgical symptomatology was noted. In particular no evidence of ulcer related dyspepsia or haematemesis and/or melaena could be elicited from our records for patients who underwent gastroenterostomy.

It has been suggested that patients who eventually develop duodenal obstruction have a greater incidence of anorexia and vomiting at the time of presentation and this might allow selection for duodenal bypass even when a barium meal appears normal[13,14]. In this study anorexia and vomiting occurred as frequently at presentation and had a similar duration in group A patients who did not progress to duodenal obstruction as in those who did. We conclude that no particular emphasis can be placed on these symptoms as prognostic indicators for subsequent duodenal obstruction in the absence of radiological evidence of duodenal narrowing.

Patients undergoing palliative surgery for carcinoma of the head of the pancreas have a short life expectancy and subsequent surgical intervention for duodenal obstruction should be regarded as a failure of surgical management. An initial combined bypass procedure appears to be associated with the same morbidity and mortality as a biliary bypass procedure alone and therefore, in the absence of an accurate method of predicting subsequent duodenal obstruction, a combined biliary and duodenal bypass procedure should be considered for all patients with this diagnosis.

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Primary lymphoma of the breast

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Fifteen patients with primary lymphoma of breast are reported from a 30-year review. Eight of the patients were diagnosed in the last 5 years of this review, suggesting either an increase in the incidence or an increasing awareness of this condition. The age range was from 17 to 77 years. All patients presented with a breast mass and nine had histologically proven axillary node involvement. One patient had Hodgkin's disease and the remainder were non-Hodgkin's lymphoma. Treatment was by a combination of surgery, radiotherapy and chemotherapy. During follow-up which varied from 4 to 20 years (median 8 years) three patients developed metachronous involvement of the opposite breast and three died from their disease. Prognosis was related to tumour histology and stage of disease. The three who died all had high grade centroblastic lymphoma, the three largest tumours and nodal involvement. Five and ten-year survivals were 85 per cent and 73 per cent respectively, better than the survival of patients for either other non-disseminated extranodal lymphomas or breast cancer.

Keywords: Breast lymphoma, prognosis, treatment

Primary malignant lymphoma of the breast is a rare condition with less than 300 reported cases[1,2]. Although criteria have been established for primary breast lymphoma[3], the disease incidence and prognosis are difficult to estimate because many series include patients who do not fulfil them. To qualify as a primary breast lymphoma there must be:

1. A close association between breast tissue and infiltrating lymphoma.
2. The absence of concurrent widespread lymphoma and no preceding extramammary lymphoma.
3. Documentation of breast as the principal organ involved and thus the primary site.

We report 15 patients with primary breast lymphoma which satisfy these criteria.

Patients and methods

A 30-year retrospective review from 1950 to 1980 of records in the Department of Pathology, University of Edinburgh revealed 15 patients with a histological diagnosis of breast lymphoma which fulfilled the criteria listed above. In each case the original haemotoxylin and eosin, and reticulin stained sections were re-examined and where required sections were recut and special stains utilized. The lymphomas were categorized according to the Rappaport and Kiel classifications[4].

Full clinical information and follow-up to the end of 1985 were available for all patients. The survival of patients with breast lymphoma was compared with that of a series of 250 patients with breast cancer[5] treated in Edinburgh during the same period using the Lee–Desu statistic[6].

Results

During the first 25 years of the review, seven breast lymphomas were diagnosed, an incidence during that period of 0·15 per cent of all breast malignancies. Within the last 5 years of the review, eight were identified giving an incidence of 0·5 per cent of all breast malignancies. The increase from 0·15 per cent to 0·5 per cent is significant ($P<0{\cdot}01$, χ^2 test).

Clinical data

All 15 patients were female with an age range of 17–77 years (mean 52). All presented with a breast mass of duration 2 weeks to 1 year (median 3 months). Ten patients had initial involvement of the left breast and five patients the right breast. Three patients subsequently developed involvement of the opposite breast, all within 3 years of diagnosis.

On examination, five of the masses were greater than 5 cm in diameter and one patient had two discrete masses palpable. Three of the tumours were fixed to skin, but none showed deep fixation. In no patient was a diagnosis of lymphoma suspected after clinical examination.

Mammograms were performed on six patients, and in four, a well-defined opacity with a halo was present. In the other two, there was an irregular mass. Fine needle aspiration cytology was performed in two patients and both were reported as suggestive of breast lymphoma. Three patients had frozen section examination, all were diagnosed as carcinomas and only on subsequent paraffin section histology was the correct diagnosis made.

A full blood count, biochemical investigations including calcium, phosphate and liver function tests, chest and pelvis X-rays and bone marrow examination were performed for all patients. Six patients had bone scans performed, four had lymphangiography and four underwent a staging laparotomy. In all patients these investigations failed to show any sign of lymphoma outside the breast and homolateral axilla.

Histology

The original diagnosis of lymphoma was confirmed in all 15 cases and none were pseudolymphomas[7]. One patient had nodular sclerosing Hodgkin's disease and the other fourteen had non-Hodgkin's lymphoma which were classified by Rappaport and Kiel classifications as shown in *Table 1*. The patient with two masses had identical histopathology in each as did all three patients who developed metachronous contralateral breast involvement. Nine patients had histologically proven homolateral axillary node involvement.

Treatment and survival

Patients were treated with various combinations of surgery, radiotherapy and chemotherapy. The chemotherapy given varied during the study period. Seven patients had a mastectomy and node sample. This includes the three patients diagnosed as having carcinoma on frozen section and four other patients with large tumours in small breasts. In the remaining eight patients the lymphoma was simply excised and axillary lymph nodes biopsied. All 15 patients received radiotherapy to the chest wall, any residual breast tissue and axilla. Five patients had postoperative chemotherapy.

Follow-up was to death or to the end of 1985 and varied from 4 to 20 years (median 8 years). Three patients died during this period from disseminated disease. They had the largest three breast lumps measuring 6·5, 8 and 12 cm in diameter, all were

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Table 1 *Classification of the 14 non-Hodgkin's breast lymphomas by Rappaport and Kiel classifications*

	No. of patients
Rappaport	
Lymphocytic	
Diffuse well differentiated	1
Diffuse poorly differentiated	1
Nodular poorly differentiated	3
Mixed lymphocytic/histiocytic	
Diffuse	1
Nodular	1
Histiocytic	
Diffuse	7
Kiel	
Low grade	
Lymphocytic	1
Centrocytic/centroblastic	5
High grade	
Centroblastic	7
Immunoblastic	1

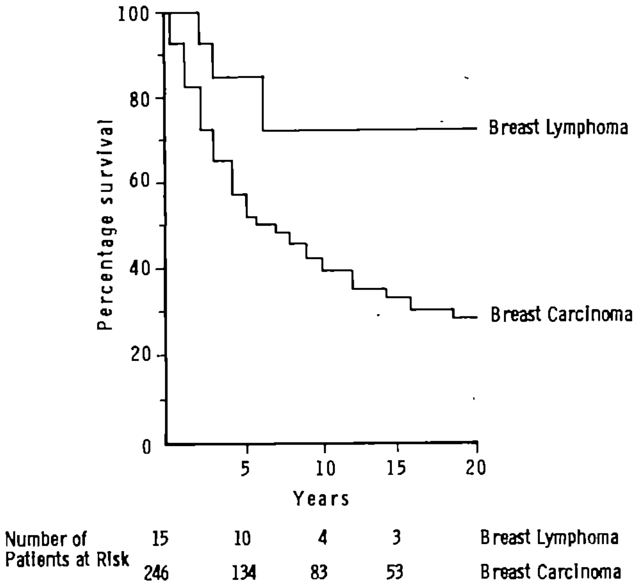

Figure 1 *This compares the survival curves of the 15 patients with breast lymphoma and a series of 250 patients with breast carcinoma treated during the same period*

high grade centroblastic lymphomas and all three had homolateral axillary node involvement. The survival curve for the 15 patients is shown in *Figure 1* and is compared with a consecutive series of patients with breast carcinoma. Patients with lymphoma had a better survival than patients with breast cancer. Because of the small numbers in the lymphoma group this difference did not quite reach statistical significance ($P = 0{\cdot}06$).

Clinical, histological and follow-up data for all 15 patients are summarized in *Table 2*.

Discussion

Although it has been suggested that breast lymphoma is one part of a multisystem involvement[4,8,9], the exclusion of patients with disease outside the breast and local axilla makes this explanation unlikely for the present series. More plausible is the belief that lymphoma arises from the periductal and perilobular lymphoid tissue which is frequently seen in the breast[8]. Actual incidence is difficult to assess[2,3] as many published series include patients with disease outside the breast. In Edinburgh, the incidence of primary breast lymphoma appears to have increased in the last few years, to comprise 0·5 per cent of all primary breast malignancies. This could be a true increase, but is more probably the result of an increasing awareness of this condition.

Peak age incidence for breast lymphomas in previous reports has been the sixth decade[1–3,8–12], but in this series there was an even distribution from the fourth to eighth decades. Despite previous indications that breast lymphomas may be more common in the right breast[10], in the present series they were more common in the left, suggesting there is no predilection for one or other breast. Involvement of both breasts is a feature of this condition, but whether synchronous or developing later does not apparently affect prognosis adversely[10]. In keeping with this, the three patients reported here who had metachronous contralateral involvement by lymphoma were all alive at follow-up.

A diagnosis of primary breast lymphoma is unlikely to be possible on the basis of clinical examination. Three of our patients had skin involvement, a feature generally regarded as diagnostic of carcinoma. Most patients presented with discrete mobile masses with no superficial or deep fixation. Mammography may suggest the diagnosis, the typical feature being a well rounded mass with a regular smooth outline surrounded by a thin perimeter of radiolucency[11]. This feature was present in four of our six patients who had mammography.

Table 2 *Clinical and histological data on the 15 patients with primary breast lymphoma*

				Pathology	
Age	Size of mass (cm)	Treatment	Follow-up	Rappaport	Kiel
17	2	LX XRT	Alive 25 years	N PD L	Low C/C-F
35	3	MX XRT	Alive 5 years	D H	High C
37	2	LX XRT	Alive 5 years	N M L/H	Low C/C-F
39	5	MX XRT	Alive 20 years	D PD L	Low C/C-D
42	6·5	MX XRT Chemo.	Died lymphoma 6 years	D H	High C
42	2	LX XRT	Alive 18 years	N PD L	Low C/C-F
43	12	MX XRT Chemo.	Died lymphoma 1 year	D H	High C
55	3	LX XRT	Alive 6 years	D WD L	Low L
58	3	LX XRT Chemo.	Died MI 1 year no lymphoma†	D H	High C
58	3	LX XRT Chemo.	Alive 4 years	D H	High I
58	3·5	MX XRT	Died O/D 7 years no lymphoma†	N S	Hodgkin's
67	8	MX XRT	Died lymphoma 2 years	D M L/H	High C
72	3	LX XRT Chemo.	Alive 10 years	N PD L	Low C/C-F
75	6	LX XRT	Alive 6 years	D H	High C
77	6	MX XRT	Died 3 years carcinoma of rectum No lymphoma†	D H	High C

LX = Lymphoma excised; MX = mastectomy; XRT = radiotherapy; Chemo. = chemotherapy; N = nodular; D = diffuse; F = follicular; H = histiocytic; L = lymphocytic; I = immunoblastic; C = centroblastic; C/C = centrocytic/centroblastic; PD = poorly differentiated; WD = well differentiated; M = mixed; NS = nodular sclerosing; O/D = overdose; MI = myocardial infarction.

†3 patients died of other causes during follow-up – none had any evidence of lymphoma at death

In the present series diagnosis was based on open biopsy and paraffin section histology. Frozen section appears unreliable in diagnosing breast lymphoma, the three patients undergoing frozen section biopsy all being reported as having poorly differentiated carcinoma. Tru-cut biopsy may also be unreliable[12]. It is relevant that the increased detection of lymphoma correlates with the decreasing use of frozen section locally and it is possible that other cases of breast lymphoma have been misdiagnosed by this technique. Fine needle aspiration cytology is now our method of choice for the diagnosis of breast lumps[13], and in the two patients where this was performed, a diagnosis of lymphoma was suggested by the cytologist. This allowed full staging investigations and planned treatment in these patients.

A number of different treatment regimens have been used in this condition[1–3,8–12,14–17]. This and other studies suggest that for small tumours localized to the breast and axilla adequate excision followed by radiotherapy is effective. Where the tumour is large a mastectomy and postoperative radiotherapy are often required, but more radical surgery is not indicated. Widespread axillary disease or high grade tumours probably benefit from the addition of chemotherapy. It is likely that a combination of coordinated treatment by our local lymphoma group and more effective chemotherapy improved the survival of patients treated during the last 10 years of this review.

It has been claimed that the size of the primary lesion and node status do not affect prognosis[1,2,17]. This is difficult to reconcile with the present data in which the only three patients who died had the three largest tumours and axillary node involvement. Prognosis also appears to be related to histology, with high grade centroblastic lymphomas having the worst prognosis. Published 5 year survival figures for primary breast lymphoma vary from 19 to 64 per cent[2,8,12,14–17]. This variation is partly related to the inclusion in some series of patients with extramammary disease at diagnosis. The 5 year survival in this series was 85 per cent which can be compared with 53 per cent for a consecutive series of breast carcinomas treated during the same period in the same centre[5] and a 41 per cent survival for a large series of patients with non-disseminated extranodal lymphomas of non-Hodgkin's type[18]. As it appears that patients with primary breast lymphoma have a better survival than either patients with breast cancer or other extranodal lymphomas, it is important that these tumours are recognized and treated appropriately.

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Preliminary results of the Nottingham breast self-examination education programme

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Between June 1979 and December 1984, 49 573 women (study population) between the ages of 45 and 64 years and living in one health district were invited to attend breast self-examination sessions as part of the DHSS 'UK Trial of Early Detection of Breast Cancer'. Of the women invited 50·2 per cent attended for education. A total of 319 breast cancers were diagnosed in the study population during this period. The tumour characteristics, patient prognostic groups and survival have been compared with a control population consisting of the 319 consecutive breast cancers diagnosed immediately before the start of the DHSS trial, in women of the same age group and living in the same health district. There has been a significant reduction in the size at presentation of operable tumours ($P < 0{\cdot}01$) and there has been a small (3·4 per cent) reduction in lymph node involvement, but this is not significant. The rates of presentation of both in situ *and advanced carcinoma have not significantly changed following the introduction of a breast self-examination education programme. At this stage no overall survival difference has been identified between the two groups but the median follow up of the study population is limited (25 months).*

Keywords: Breast cancer, screening, self-examination

The Nottingham breast self-examination education programme was set up in 1979 as part of the DHSS 'Trial of Early Detection of Breast Cancer'[1]. This programme consisted of inviting all women aged between 45 and 65 years in the South Nottingham health district for education in breast self-examination. A self-referral clinic was provided for women within this population who detected a breast abnormality.

In the DHSS trial one other centre is examining the value of breast self-examination education and two centres are investigating mammographic screening of asymptomatic women. Four other health districts in the UK act as control populations; in these areas no special efforts are directed towards early detection of breast cancer. In this preliminary report of the Nottingham experience, from June 1979 to December 1984, we have made a retrospective comparison of the tumour characteristics and survival of all patients diagnosed as having breast cancer with a control population. The control group consists of an identical number of the consecutive breast cancer patients presenting in the South Nottingham health district immediately before the start of the DHSS trial.

Patients and methods

The Nottingham breast self-examination programme has been described previously[1–3]. Briefly, at the outset of the trial a register was compiled from the Family Practitioner Committee's records of all women between the ages of 45 and 64 years, together with those who would attain this age during the 7 years' duration of the trial, who lived in the area then covered by the old South Nottingham health district. These women were invited, by a standard letter sent on behalf of their general practitioner, to attend an education session given by specially trained nurses. This consisted of a talk and a short film followed by a discussion session, particular emphasis being placed on the physical and visual signs of breast cancer. The women were encouraged to refer themselves to an associated open-access clinic should they subsequently find an abnormality. On attending the self-referral clinic the patients were examined by the same nursing staff and two-view mammography (craniocaudal and lateral oblique) was performed by the radiographer. All mammograms were checked once each week by the consultant radiologist (E.J.R.). Patients with suspicious clinical or mammographic abnormalities were reviewed by the clinic doctor who was a member of a surgical breast cancer team. Suspicious lesions were then referred for biopsy.

The tumour characteristics of 319 patients with breast cancer were prospectively recorded. Sixty-nine per cent of the patients with breast cancer in the study population were referred to one surgical team (R.W.B.) and complete information was available on all these patients. Tumour size has been measured as the maximum tumour diameter in the fresh mastectomy specimen, where this was not available the pathological size after tumour fixation was recorded. Tumour histological grade was reviewed by one pathologist (C.W.E.) using a modification of the Bloom and Richardson criteria[4] and lymph node involvement was assessed by histology.

A patient was classified as having advanced breast cancer if she fell into one of the three following categories: (1) locally advanced, tumour size >5 cm diameter or clinically inoperable; (2) patients with distant metastases at presentation; (3) patients dying from breast cancer within 3 months of diagnosis.

The tumour characteristics of the 319 patients in the study population have been compared with those of the 319 consecutive breast cancers diagnosed immediately before the start of the DHSS trial, in patients in the same age group and living in the same health district. The control population was derived retrospectively from the Cancer Registration Bureau (Trent Regional Health Authority) records and was supplemented by searching the pathology department's records of the three local general hospitals (Nottingham's City, General and University Hospitals), thus enabling all the breast cancers diagnosed in the 5 years before the trial to be identified.

One hundred and fifty nine of the patients with operable carcinoma in the study group and 123 patients in the control group were treated under the care of a single consultant surgeon (R.W.B.) and had been entered into the Nottingham/Tenovus breast cancer series. A range of prognostic factors had been prospectively recorded on all these patients allowing their stratification into prognostic groups by the Nottingham prognostic index using tumour size, histological grade and lymph node stage[5]. This allows the identification of three groups of patients with differing survival probabilities: the 'good', 'moderate' and 'poor' prognostic groups with 88, 69 and 22 per cent 5-year survival rates respectively. The proportions of patients in each of the prognostic groups have been compared in the study and control populations.

The work described in this paper was presented to the Surgical Research Society in January 1986

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Statistics

The correlations between tumour size, lymph node involvement and prognostic groups were examined within the two groups by χ^2 analysis. Actuarial life table analysis has been used to compare survival data.

Results

Between June 1979 and December 1984, 49 573 women (study population) were invited to attend breast self-examination education sessions: 24 922 (50·2 per cent) attended. During this time 2706 women referred themselves to the open-access clinic.

No significant difference in the rate of carcinoma *in situ* presentation was noted between the study and the control population, being 4·1 and 3·1 per cent respectively (*Table 1*).

Tumour size in the fresh mastectomy specimen was available for 69 per cent of the operable carcinomas in the study population and 65 per cent of the controls. In the remainder, where size was available, it was measured after formalin fixation of tumour tissue. Significantly more small operable cancers were detected in the study population than in the control group (*Table 1*). The median size of the operable cancers was 2·0 cm in the study group and 2·3 cm in the control group. No breast cancer under 5 mm in size was detected in either population, 14 cancers between 5 and 10 mm were detected, 9 in the study group and 5 in the control group.

There was no significant difference in the lymph node involvement at presentation between the two groups, 57·4 per cent of the study group and 54·0 per cent of the controls were node negative (*Table 2*).

The rate of presentation of advanced breast cancer remained high and was not significantly different between the two groups; 19·7 per cent and 16·9 per cent for the study and control groups respectively (*Table 1*).

The life table curves comparing the survival data of the study and control populations are shown in *Figure 1*. The study group has been followed for a median of 25 months (range 12–72 months), whereas the control group has a median follow up of 84 months (range 72–126 months). At this stage no significant difference in survival can be identified.

Survival of patients within the study population has been examined after subgrouping on attendance for education (*Figure 2*) and on utilization of the self-referral clinics (*Figure 3*). There are significant survival advantages for both the 'educated' and the 'self-referred' subgroups when compared with the 'not educated' and 'GP referred' groups respectively.

Table 1 *Tumour size distribution at presentation*

		Operable invasive carcinoma			
	Carcinoma *in situ*	≤2·0 cm	2·0–5·0 cm	Size not known	Advanced cancer
Study population ($n=319$)	13	132	99	12	63
Control population ($n=319$)	10	106	133	16	54
Statistical significance	n.s.	$\chi^2=7{\cdot}69$ (1 d.f.) $P<0{\cdot}01$		—	n.s.

Table 2 *Lymph node involvement at presentation for operable carcinoma*

	Lymph node involvement		
	Node negative	Node positive	Not known
Study population ($n=244$)	124	92	28
Control population ($n=249$)	108	92	49
Statistical significance	$\chi^2=0{\cdot}49$ (1 d.f.) n.s.		—

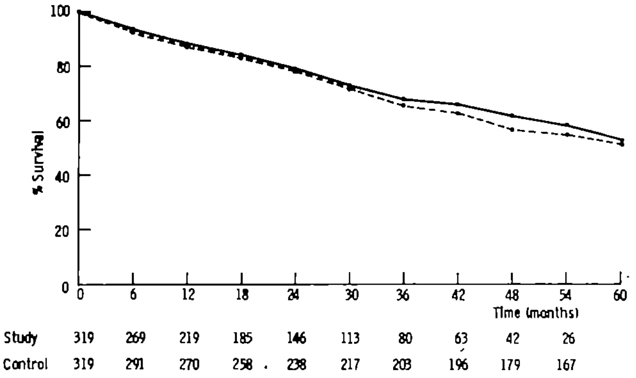

Figure 1 *Survival: study population* (– – –) versus *control* (———). *Population: all cases.* $\chi^2=0{\cdot}4$, *1 d.f.*, P *n.s.*

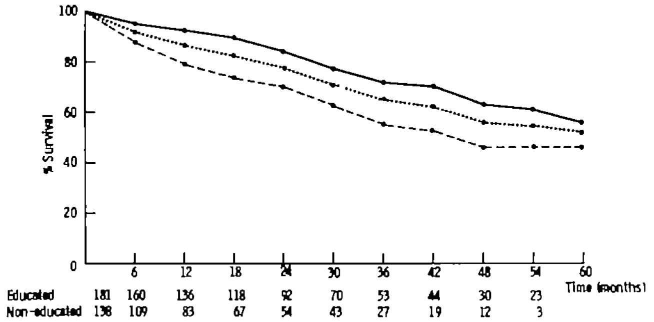

Figure 2 *Survival: study population, 'educated'* (———) versus *'not educated'* (– – –); *all study group* (· · · ·). $\chi^2=9{\cdot}42$, *1 d.f.*, $P<0{\cdot}01$

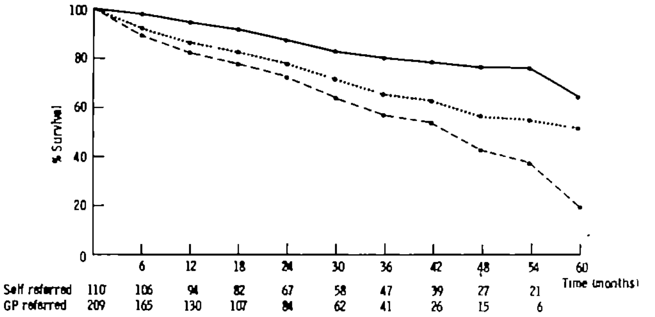

Figure 3 *Survival: study population, self-referred* (———) versus *GP referred* (– – –); *all study group* (· · · ·). $\chi^2=20{\cdot}05$, *1 d.f.*, $P<0{\cdot}001$

A total of 282 patients in the study and control populations had been entered into the Nottingham/Tenovus series and it was possible to stratify these patients into three prognostic groups. The prognosis of the 23 patients with carcinoma *in situ* is extremely favourable and these patients have been analysed with those in the 'good' prognostic group. Conversely, the prognosis of the 117 patients with advanced breast cancer is extremely poor and these patients have been analysed with the 'poor' prognostic group (*Table 3*). There is a shift towards tumours with better prognostic features in the study population with 5·4 per cent less patients in the 'poor' prognostic group and 3·1 per cent more in the 'good' prognostic group compared with the controls. This trend does not reach statistical significance.

Discussion

Personal invitation of women to attend breast self-examination education resulted in approximately half of the women attending education sessions. This form of invitation was

Table 3 *Distribution by Nottingham prognostic index groups of 422 patients treated by one consultant (R.W.B.) (5-year survival probability of 'good', 'moderate' and 'poor' groups is 88, 69 and 22 per cent respectively)*

	Prognostic group		
	Good + carcinoma *in situ*	Moderate	Poor + 'advanced' cancer
Study population ($n = 235$)	55 (23·4)	91 (38·7)	89 (37·9)
Control population ($n = 187$)	38 (20·3)	68 (36·4)	81 (43·3)
Statistical significance	$\chi^2 = 1{\cdot}37$, 2 d.f., n.s.		

Figures in parentheses are percentages

decided on after the failure of an initial local advertising and leaflet campaign, which has also been noted by the other DHSS breast self-examination education centre[6]. A number of invitations were returned because of incorrect addressing and we have identified inaccuracies in the Family Practitioner Committee's register. When this is taken into consideration, the attendance rate was almost 60 per cent of those who have received their invitation.

One hundred and ten (34·5 per cent) of the 319 cancers in the study population were diagnosed in patients attending the self-referral clinics, the remainder were diagnosed via the general practitioner and surgical out-patient clinics. One hundred and eighty one (56·7 per cent) of the 319 cancers occurred in patients who had attended breast self-examination education.

The prognostic tumour characteristics of operable breast cancer in the study population have improved with significantly increased numbers of small operable tumours. There is also a trend towards less nodal involvement at presentation. However, the rate of diagnosis of carcinoma *in situ* has not increased nor has the rate of advanced breast cancer presentation diminished.

Recent reports of the results of mammographic screening[7–9] have supported the New York Health Insurance Plan study data[10] showing a reduction of mortality from breast cancer of the order of 30 per cent in patients in the same age group as this study. At this stage we have failed to show a survival benefit for women following a breast self-examination education programme when compared with a control group who received no specific instruction. However, the changes in the distribution of patients stratified by prognostic groups is small but encouraging and suggests that there may be a small long-term benefit demonstrable for the whole study population following breast self-examination education. Very few deaths occur in the 'good' prognostic groups in the first few years of follow up, most of the early breast cancer mortality occurring in the 'poor' and 'moderate' prognostic groups. Therefore a shift towards better prognostic features may be reflected in a survival benefit after longer term follow up, i.e. 10–20 years. We have calculated that an improvement in prognostic factors of the magnitude found in this report would require a study population approximately six times larger before a significant survival difference could be detected for the whole of this population after an equivalent follow up period.

Those patients developing breast cancer who had attended education have a better prognosis than those who did not attend for education. Those patients utilizing the self-referral clinics have a markedly better survival than those who have used conventional referral channels. This suggests that breast self-examination adequately performed and acted upon, may result in a significant survival advantage. The problem is one of motivation of the population to perform breast self-examination and to attend early for medical advice once an abnormality has been detected. Swedish mammographic screening studies have reported attendance rates of up to 90 per cent[7]; if compliance rates of this order of magnitude could be achieved for breast self-examination programmes, then it is possible that significant survival improvements would be detected. Conversely, the poor motivation of women to attend for breast screening may adversely affect the results of future mammographic screening programmes in the UK.

We would propose that breast self-examination education should form part of a breast screening programme based on mammography. The sensitivity of mammography alone can be as high as 95 per cent[11], but this inevitably means that some breast cancers will be missed and teaching breast self-examination as a supplement may result in the detection of 'interval' cancers at an earlier stage.

This report is based on the early results of the Nottingham breast self-examination education programme and a comparison has been made with a historical control population. It is possible that part of the effect noted may be accounted for by a general increase in awareness of breast symptoms, independent of the breast self-examination programme. The DHSS trial will compare the Nottingham results with data from contemporaneous control populations and the early results of this trial should be available by 1988. This study provides an excellent opportunity finally to assess the value of breast self-examination in breast cancer screening and there is no other trial being conducted on this scale which is able to provide the same information. For this reason, it is important that the ability to self-refer in this study should be continued for at least a further 5 years. In addition, in view of the fact that the potential benefit of breast self-examination may only be detectable after a prolonged period of time, this population requires detailed follow up for a further 10–15 years to obtain definitive data.

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Cyclical mastalgia: clinical and mammographic observations in a screened population

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The incidence of cyclical mastalgia in well women presenting for breast screening was 69 per cent. The incidence of cyclical mastalgia increases with age up to the menopause. There was a higher incidence of 'high risk' mammographic patterns and a lower incidence of 'low risk' patterns, according to the Wolfe classification, in women with cyclical mastalgia compared with the rest of the screened population. This finding correlated with the severity, duration and need for treatment. The differences in breast pattern did not persist after the menopause. The question of whether or not cyclical mastalgia can be regarded as a risk factor for breast cancer is uncertain and needs further evaluation.

Keywords: Mastalgia, mammography, breast disease, breast cancer risk

Pain in the breast is a common complaint. Preece *et al.*[1] have suggested a useful working classification of breast pain based on clinical presentation. They divided their patients into two major groups, those with cyclical pain and those with non-cyclical pain. Atkins (1938)[2] and Patey (1949)[3] both concluded that the majority of women complaining of pain in the breast were neurotic. Preece *et al.*[4], however, found no evidence of increased neuroticism on formal testing of women with breast pain. The frequent response of cyclical mastalgia to hormonal therapy[5–8] suggests a hormonal basis for this condition. However, hormonal studies in these patients have produced conflicting and confusing results[9–11]. It may be that a heterogeneous collection of hormonal variations may produce the same end point in terms of the patients' pain.

Wolfe, in 1967[12], described four breast patterns on mammography which he designated N_1, P_1, P_2 and DY. In the N_1 type the breast is composed primarily of fat, often with a trabeculated appearance. Prominent ducts occupying one quarter or less of the breast volume denote the P_1 type, and more extensive ductal prominence the P_2 type. The DY type has a dense and homogeneous stromal pattern without the prominent duct pattern as the dominant feature. In 1976 he demonstrated an association between the patterns and the risk for breast cancer. In one group he found a relative risk of 37 for the DY group and 14 for the P_2 group compared with N_1 [13]. In a second cohort[14] the magnitude of risk was lower, DY having a 21 times risk and P_2 a 7 times risk, compared with the N_1 pattern.

The association of the P_2 and DY patterns with an increased risk of breast cancer has been corroborated by a number of studies[15–20], although some workers have failed to find such a correlation[21–24]. This lack of concordance between studies might result from methodological differences[23], particularly with regard to classification of the mammographic patterns[25,26].

Wellings and Wolfe found a good correlation between the radiological patterns and the histological finding[27]. Breasts with a high risk mammographic pattern had histological features such as epithelial atypia associated with an increased risk of breast cancer. Moskowitz *et al.*, however, were unable to identify any consistent relationship between mammographic patterns and histology[22].

Variation in breast pattern with age, menopausal status[16,19,28–30], parity[31,32], and the use of oral contraception[32,33] suggests some hormonal influence on the mammographic pattern.

The current study was undertaken to investigate epidemiological features of cyclical mastalgia in a population of 'well women' from a breast screening programme. A second aim was to determine if there was any relationship between cyclical mastalgia and breast pattern, as both come under hormonal influences.

Patients and methods

The University of Liverpool Departments of Surgery and Radiodiagnosis have been running a breast screening service since 1979. Self-referred women over the age of 35 years were eligible for screening. The unit examined well women only, patients who suspected that they had some serious breast pathology being referred back to their family practitioner for early referral to a surgical breast clinic.

Each woman completed, with the help of a nurse, a detailed questionnaire on her past medical, obstetric and menstrual history; symptoms related to the breasts and family history of breast disease. There were questions which related to both current and past breast pain.

Cyclical pain was scored in relation to frequency and to severity. A four point scale was used for both parameters. For frequency, the scoring system was 1 = never, 2 = every 4–6 months, 3 = every 2–3 months and 4 = every cycle. For severity, the scoring was 1 = no symptoms, 2 = mild symptoms regarded by the patient as of no importance, 3 = moderate symptoms causing the patient distress but not preventing her at any time from doing what she wanted, 4 = severe symptoms interfering with her life.

A past history of the occurrence and severity of pain was recorded for each decade up to 40 years old, and for each 5 year period thereafter until the menopause. A record was also made of any past or current treatment for breast pain. Current non-cyclical pain was also recorded. For any given question a small number of patients was unable, or unwilling, to supply an answer.

The women's breasts were then examined by the nurse and mammography performed in craniocaudal and lateral oblique projections. The mammograms were interpreted by one radiologist (G.H.W.) and were categorized according to Wolfe's classification. Coding was performed on two occasions. The answers to the questionnaire and the mammographic findings were encoded and stored in the University of Liverpool IBM 3083 computer for later analysis.

The data in this study were derived from the first 5319 women screened. Analysis of the results has been carried out using the Statistical Package for the Social Sciences-X programme pack (SPSS-X). Statistical significance was analysed using the χ^2 test.

Results

The 5319 patients studied ranged in age from 35 to 75 years with a mean age of 46 years.

Of the 5087 women on whom information concerning menstrual status was available 2174 were premenopausal, 762 were perimenopausal and 2151 were postmenopausal. In the postmenopausal group, 1748 women were able to give a clear and reliable history concerning cyclical mastalgia before the menopause.

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Non-cyclical pain

Non-cyclical pain was present in 173 premenopausal women (7·9 per cent) and in 151 postmenopausal women (7·0 per cent). There was no significant statistical difference in the incidence of non-cyclical pain between these two groups.

There was also no statistical difference between the breast pattern of women with non-cyclical breast pain and women without breast pain within the same menstrual category.

Cyclical pain

A total of 2936 pre- and perimenopausal women answered questions on cyclical pain. Of these women, 2024 (68·9 per cent) reported grade 3 or 4 breast pain every 2–3 months or more frequently. In response to questions on their history, 23 per cent reported that they had had cyclical mastalgia when less than 20 years of age; the incidence rose to 45 per cent by age 40–44 years.

Table 1 shows the distribution of breast pattern in premenopausal and perimenopausal women, with and without a history of cyclical breast pain. There is a highly significant difference in the distribution of breast patterns between the two groups. Women with breast pain had a higher incidence of P_2 pattern and a lower incidence of N_1 pattern than women with minimal or no pain.

Only 3·4 per cent of all pre- and perimenopausal women had ever received any treatment for this symptom. As *Table 2* shows, patients who had received treatment have a higher incidence of DY with a correspondingly reduced incidence of N_1 than those without treatment. The difference did not, however, reach statistical significance. Treatment included simple analgesics, diuretics and hormonal preparations. It is clear from *Table 3* that the longer the duration of pain in a cycle, the more likely the patient was to have a high risk breast pattern. This was mainly an increase in the DY pattern. A correlation was noted between parenchymal patterns and the patients' subjective estimates of the severity of the pain (*Table 4*), with an increasing incidence of DY and P_2 and a corresponding fall in N_1 when symptoms were moderate or severe in intensity. There is no association between breast pattern and a history of pre-menopausal cyclical mastalgia in the postmenopausal woman.

Table 1 *Relationship of breast patterns to cyclical mastalgia in peri- and premenopausal women*

	Pain		
Breast pattern	None or occasional n (%)	Frequent or every cycle n (%)	Total n (%)
N_1	163 (17·9)	236 (11·7)	399 (13·6)
P_1	73 (8·0)	151 (7·5)	224 (7·6)
P_2	116 (12·7)	356 (17·6)	472 (16·1)
DY	560 (61·4)	1281 (63·3)	1841 (62·7)
Total	912 (100)	2024 (100)	2936 (100)

$\chi^2 = 27{\cdot}73$, d.f. $= 5$, $P < 0{\cdot}0001$

Occasional pain refers to pain less frequently than every 2–3 months, while frequent pain occurs every 2–3 months

Table 2 *Relationship of breast pattern to treatment for cyclical mastalgia*

Breast pattern	No treatment n (%)	Treatment n (%)
N_1	283 (14)	11 (11)
P_1	135 (7)	9 (9)
P_2	285 (14)	12 (12)
DY	1367 (66)	72 (69)
Total	2070	104

$\chi^2 = 1{\cdot}89$; d.f. $= 5$; $P = 0{\cdot}59$

Table 3 *Relationship of breast pattern to current duration of pain during a menstrual cycle*

Breast pattern	No pain n (%)	1–3 days n (%)	4–7 days n (%)	7+ days n (%)
N_1	93 (16)	155 (14)	39 (9)	5 (6)
P_1	42 (7)	73 (7)	24 (6)	5 (6)
P_2	65 (11)	154 (14)	67 (16)	11 (14)
DY	369 (65)	717 (65)	289 (69)	60 (74)
Total	569	1099	419	81

$\chi^2 = 18{\cdot}82$; d.f. $= 7$; $P = 0{\cdot}03$

Table 4 *Relationship of women's subjective estimate of severity of pain during current menstrual cycles to breast pattern*

Breast pattern	None (grade 1) n (%)	Mild (grade 2) n (%)	Moderate or severe (grade 3 or 4) n (%)
N_1	96 (17)	181 (14)	17 (6)
P_1	42 (7)	83 (6)	19 (7)
P_2	66 (11)	185 (14)	46 (17)
DY	377 (65)	868 (66)	193 (70)
Total	581	1317	275

$\chi^2 = 28{\cdot}06$; d.f. $= 6$; $P = 0{\cdot}0009$

Discussion

The present study has confirmed that breast pain is a common problem. Despite an incidence of up to 45 per cent only 3·4 per cent of women had ever sought treatment for cyclical mastalgia. There was no clear symptomatic distinction between women who had presented with cyclical mastalgia and received treatment and those women with cyclical pain who do not receive treatment. Certainly, no apparent difference exists in the duration or frequency of symptoms nor in the patient's reported perception of the severity of their symptoms.

In view of the highly subjective nature of the assessment of severity of pain, it is perhaps surprising that such a marked correlation exists between the breast pattern and the patient's estimate of severity. There is also a similar correlation between breast pattern and the duration of pain.

It is unclear why the relationship between a history of cyclical mastalgia and breast pattern disappears in the postmenopausal women. The lower incidence of DY pattern in this age group is in keeping with other studies[16,19,28,29]. This change in pattern distribution has been attributed to the change in hormonal balance at menopause. Cyclical mastalgia resolves at menopause[34]. It could be postulated that a common denominator which is hormonal in nature results in the involution of the DY pattern after the menopause and the disappearance of cyclical mastalgia.

Benign breast disease is a vague entity, but studies have shown a relationship between a history of 'fibroadenosis' and the subsequent development of breast cancer[35–38]. The relationship between 'fibroadenosis' and cyclical mastalgia is equally unclear but a certain overlap does exist[34]. No study to date, however, has reported any increased risk of breast cancer in patients with cyclical mastalgia.

There is a clear relationship in the present study between a history of cyclical mastalgia and mammographic patterns (P_2 and DY) which are associated with an increased risk of breast cancer. This applies only before the menopause. As studies on this same screening population[28] have found high incidences of P_2 and DY (16·4 and 57·7 per cent respectively) in the 40–49-

year-old group as a whole, the apparent association may not be significant. A need exists for a careful scrutiny of patients with cyclical mastalgia to establish whether or not a real increased risk of the development of breast cancer exists.

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Predictive power of progesterone receptor status in early breast carcinoma

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Progesterone receptor status (PgR) and oestrogen receptor status (ER) were examined in 332 women with stage I–II breast carcinoma treated at a single centre either by simple mastectomy with (n = *283) or without* (n = *6) axillary clearance, or by segmental mastectomy with* (n = *18) or without* (n = *25) axillary clearance and radiotherapy; median follow-up time was 40 (range 10–60) months. Neither the concentration nor the presence of PgR related to either disease-free interval or survival. However both the presence and the concentration of ER were found to be associated with a longer disease-free interval amongst patients with stage II tumours* (P < *0·01). From this study it appears that progesterone receptor status does not predict outcome in early breast carcinoma.*

Keywords: Breast cancer, progesterone receptor, oestrogen receptor

Since the first reports of the identification of oestrogen receptors in breast tumours and the subsequent prediction of response to endocrine manipulation[1,2], breast tumour oestrogen receptor status (ER) has been found to predict not only response to endocrine treatment[3–6], but also disease-free[6–10] and overall survival[5,6,11,12]. Experimental data suggest that the synthesis of progesterone receptors in human breast carcinoma cells is oestrogen dependent[13], and that progesterone receptor status (PgR) might also predict outcome in breast carcinoma, perhaps partly as a measure of tumour differentiation[14]. Although Maguire and his colleagues have advocated that PgR may be of greater significance than ER[15], others have failed to confirm that PgR has any prognostic significance in patients with breast carcinoma[16,17]. We have measured both tumour PgR and ER in patients with UICC stage I and II primary breast carcinoma[18] and have analysed the follow-up data to assess the possible prognostic significance of PgR amongst these patients.

Patients and methods

We treated 332 patients with UICC stage I or II tumour resected between July 1981 and June 1985 inclusive either by simple mastectomy with ($n = 283$) or without ($n = 6$) axillary clearance, or by segmental mastectomy with ($n = 18$) or without ($n = 25$) axillary clearance plus radiotherapy. Axillary clearance was not performed in 31 patients for technical reasons, for instance during segmental mastectomy for a medial tumour. Axillary lymph node status was thus determined in 301 patients.

Immediately after resection samples of primary tumours were snap frozen and stored in liquid nitrogen at −196°C, then transported from Southampton to the Breast Cancer Unit of the Tenovus Institute for Cancer Research in Cardiff for receptor assay. Absolute quantitative levels of both PgR and ER of the tumour samples were determined by the dextran-coated charcoal technique[19], and results were expressed in fmol/mg cytosol protein. Levels of 5 fmol/mg or below were considered negative.

Quantitative values of receptor levels were expressed as logarithms of receptor concentrations to adjust for skewness in the distribution of receptor levels; the distributions of positive log PgR and positive log ER were both normal. Life table plots for disease-free survival and survival from first recurrence were constructed by the method of Kaplan and Meier[20], and heterogeneity between receptor groups assessed by the log rank test. Disease-free survival plots were drawn only for those patients whose axillary lymph node status had been determined. Cox's proportional hazards technique was applied to evaluate the independent association between each prognostic variable listed in *Table 1* and the patient outcome, and to compile odds ratios as a measure of this association for each prognostic variable[21]. The extent to which each odds ratio was found to differ from 1 thus represents the relative risk of recurrence associated with each prognostic variable. Pearson's rank correlation coefficient and the χ^2 test were used to supplement this analysis. All statistical tests were computed using the BMDP programs P1L and P2L[22].

Results

The 332 patients were divided into three separate groups on the basis of absolute PgR values as displayed in *Table 1*. The distribution of all clinical features listed was similar amongst the three PgR groups. The life tables plotted in *Figures 1–3* for disease-free survival and survival from first recurrence amongst

Table 1 *Clinical features of 332 patients with early breast carcinoma and either negative, low or high positive progesterone receptor status*

	Negative ($n = 116$)	Low (6–800) ($n = 119$)	High (>800) ($n = 97$)
Age (years)			
Median (range)	62 (34–81)	57 (30–85)	57 (34–89)
Menopausal status			
Premenopausal	38	49	34
Postmenopausal	78	70	63
Primary treatment			
Wide resection	17	16	10
Mastectomy	99	103	87
Adjuvant treatment			
Chemotherapy	9	8	7
Tamoxifen	7	8	11
Both	4	4	4
Histology			
Ductal	100	109	86
Lobular	7	7	11
Other	9	3	0
Nodal status			
Nil	62	73	44
1–3	26	23	36
>3	14	11	12
Unknown	14	12	5
ER			
Negative	44	41	31
6–100	28	43	22
>100	44	35	44
Follow-up (months)			
Median (range)	28 (4–60)	21 (6–59)	24 (4–59)

ER, oestrogen receptor status
Receptor levels in fmol/mg cytosol protein

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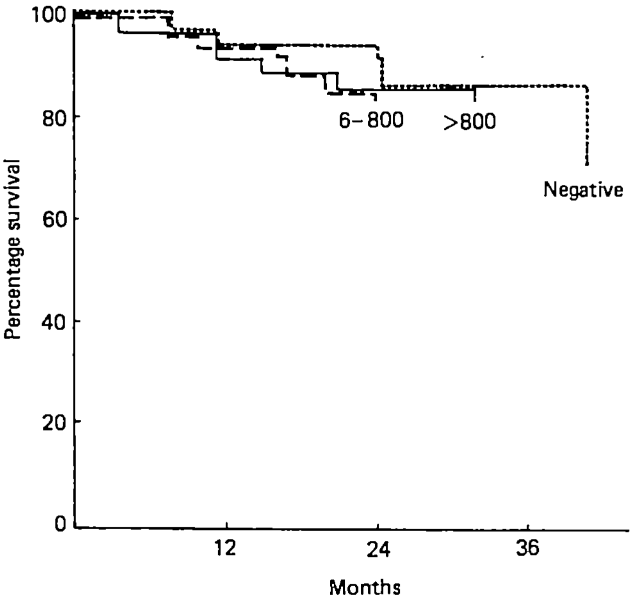

Figure 1 *Disease-free survival curves of 179 axillary node negative patients with either negative, low or high positive PgR. There were 62, 73 and 44 patients in each respective PgR group.* P>0·50, *log rank test*

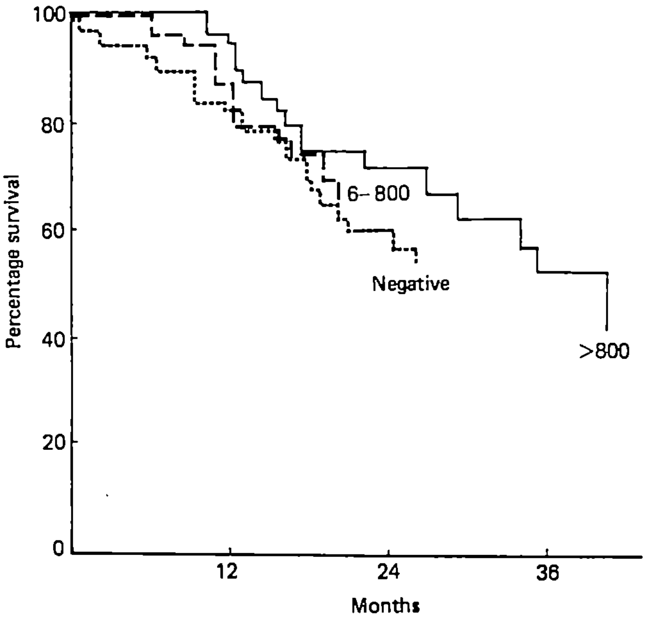

Figure 2 *Disease-free survival curves of 122 axillary node positive patients with either negative, low or high positive PgR. There were 40, 34 and 48 patients in each respective PgR group.* P>0·50, *log rank test*

the three PgR groups show no significant heterogeneity between the groups, suggesting no relation between PgR and survival.

The 332 patients were also divided into three groups on the basis of absolute ER values as displayed in *Table 2*. Postmenopausal women positive for ER were found to have higher absolute ER values than premenopausal women positive for ER ($\chi^2 = 40{\cdot}7$, d.f. $= 1$, $P < 0{\cdot}001$).

Figure 4 plots the disease-free survival of 179 lymph node negative patients amongst the three ER groups. All three ER groups did well relative to the 122 lymph node positive patients (see *Figure 5*), but despite heterogeneity no clear relation between ER and disease-free survival is apparent. In *Figure 5* the disease-free survival plot of lymph node positive patients amongst three ER groups shows positive ER associated with a significantly longer disease-free survival (log rank test, $P < 0{\cdot}02$), an association which is most obvious amongst the group with high absolute ER values (<100 fmol/mg cytosol protein).

The absence of association between PgR and outcome despite such an association for ER was reflected by an absence of correlation between PgR and ER; Pearson's rank correlation coefficient (r) for absolute receptor values of PgR and ER amongst all 288 patients with either positive PgR and ER was 0·14 ($P < 0{\cdot}10$). The absence of even a qualitative correlation is

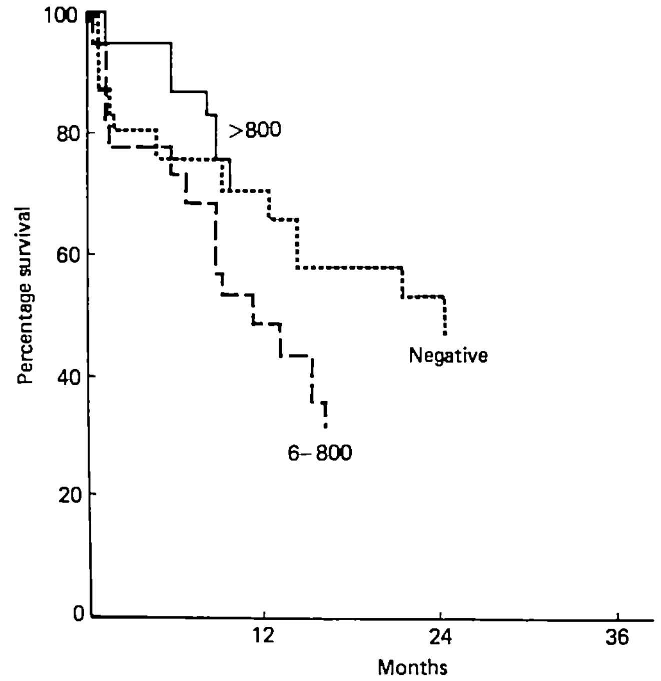

Figure 3 *Overall survival curves of 65 patients with either negative, low or high PgR from the time of first local or distant recurrence. There were 24, 23 and 18 patients in each respective PgR group.* P<0·05, *log rank test*

Table 2 *Clinical features of 332 patients with early breast carcinoma and either negative, low or high positive oestrogen receptor status*

	Negative ($n = 116$)	Low (6–100) ($n = 93$)	High (>100) ($n = 123$)
Age (years)			
Median (range)	53 (30–85)	53 (34–83)	64 (35–89)
Menopausal status			
Premenopausal	52	52	17
Postmenopausal	64	41	106
Primary treatment			
Wide resection	17	12	14
Mastectomy	99	81	109
Adjuvant treatment			
Chemotherapy	23	0	1
Tamoxifen	4	7	15
Both	1	6	5
Histology			
Ductal	102	79	112
Lobular	7	10	8
Other	7	4	3
Nodal status			
Nil	68	45	66
1–3	26	22	37
>3	14	12	11
Unknown	8	14	9
PgR			
Negative	44	28	44
6–800	41	43	35
>800	31	22	44
Follow-up (months)			
Median (range)	25 (4–60)	20 (6–59)	26 (4–60)

PgR, progesterone receptor status
Receptor levels in fmol/mg cytosol protein

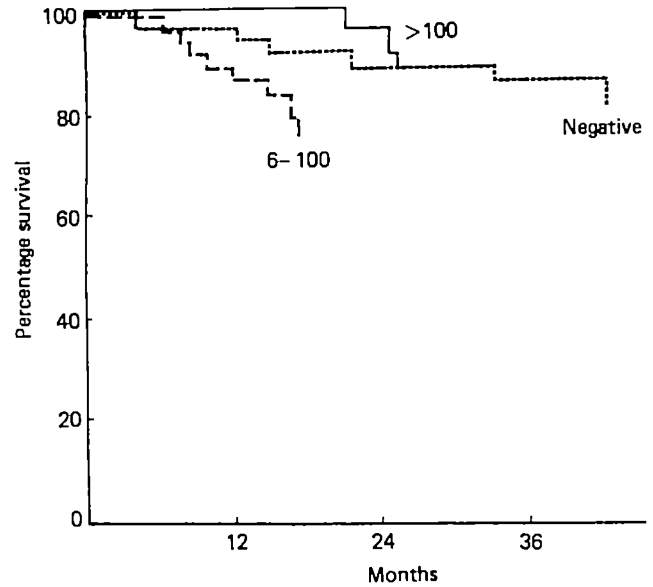

Figure 4 *Disease-free survival curves of 179 axillary node negative patients with either negative, low or high positive ER. There were 68, 45 and 66 patients in each respective ER group.* P<0·05, *log rank test*

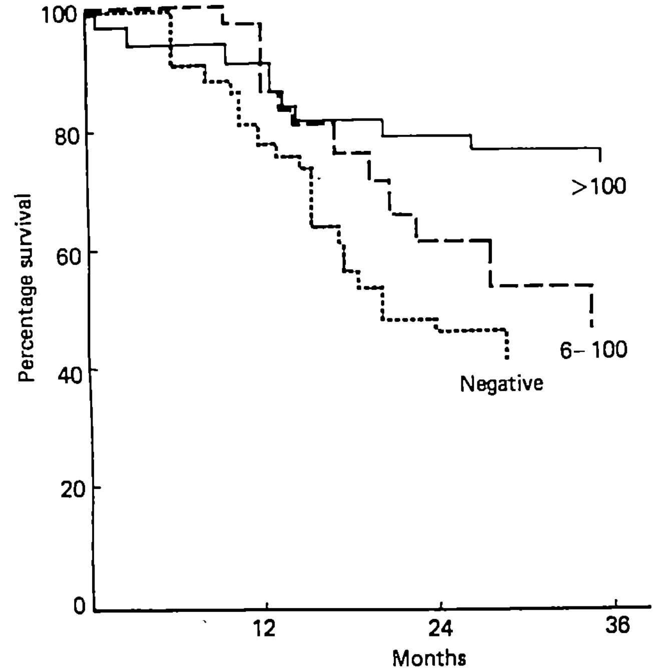

Figure 5 *Disease-free survival curves of 122 axillary node positive patients with either negative, low or high positive ER. There were 40, 34 and 48 patients in each respective ER group.* P<0·01, *log rank test*

evident from inspection of the distribution of ER amongst PgR groups and vice versa in *Tables 1* and *2* ($\chi^2=8{\cdot}6$, d.f.=4, $P<0{\cdot}05$).

Cox's proportional hazards technique enabled us to determine the independent association of absolute PgR and ER with disease-free survival by multiple regression analysis. All clinical features listed in *Tables 1* and *2* were examined by this technique to eliminate interactions between the various features that might have contributed to the findings in *Figures 1–6*. The odds ratios listed in *Table 3* represent the independent associations of these features with disease-free survival. PgR was again found to have no significant association with outcome. Age, menopausal status and adjuvant treatment were all found to have insignificant associations with disease-free survival, but the association of ER with outcome was confirmed.

Discussion

The three life table plots for the three PgR groups in *Figures 1–3* do not show an obvious relationship between PgR and outcome in our patients who presented with either stage I or II breast carcinoma. The other clinical features listed in *Table 1* were distributed in an equivalent manner between the three PgR groups; it is therefore unlikely that one of these clinical features might have obscured any association between PgR and outcome. The application of Cox's proportional hazards technique to our data has confirmed the absence of such an association by excluding the effect of other clinical features from any possible relationship between PgR and outcome.

The absence of an association between PgR and outcome despite such an association for ER was borne out by an absence of correlation between PgR and ER. Data from 35 other reports representing studies on over 9000 patients with breast carcinoma have shown that PgR and ER are both positive more often than only PgR or ER[14], but in these reports the proportion of patients positive for both PgR and ER varied from 16 to 78 per cent. Perhaps progesterone receptor synthesis in breast carcinoma cells is not as dependent on the presence and mediation of oestrogen receptors as has been suggested[23]. Our data in *Table 1* agree with other studies in that there appears to be no relationship between PgR and age, menopausal status, or lymph node status[14,16]. The strong association between PgR and disease-free survival reported by Clark *et al.* for patients with stage II breast carcinoma was based on a series of 311 patients of whom only 189 patients had PgR assays done by a sucrose density gradient method[15]. Others have found positive PgR to be associated with both a longer disease-free and overall survival[5,6,14]. Despite the reports in which such an association

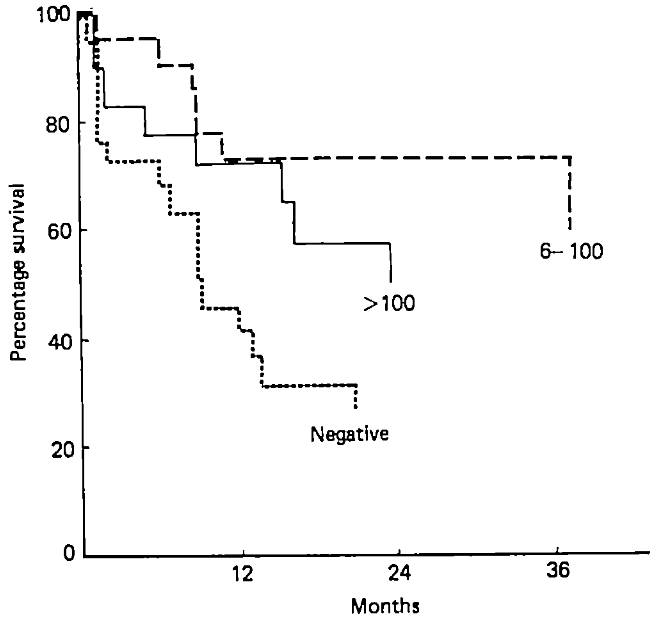

Figure 6 *Overall survival curves of 65 patients with either negative, low or high ER from the time of first local or distant recurrence. There were 25, 22 and 18 patients in each respective ER group.* P<0·02, *log rank test*

Table 3 *Odds ratios relating various clinical features to disease-free survival in early breast carcinoma*

Variable	Odds ratio (no change in risk = 1)	*P* value
Age	1·0192	0·2938
Menopausal status	1·2150	0·6528
Adjuvant chemotherapy	0·5027	0·1310
Adjuvant tamoxifen	0·9336	0·8728
Histology	0·5347	0·2984
Nodal status	4·2749	0·0001
ER	0·4936	0·0124
PgR	1·1792	0·5418

has not been found[14,16,17], it is probably reasonable to assume that there is a bias in publication towards positive findings, and that the apparent weakness of this association may not have been accurately represented by publications to date.

Acknowledgements

We thank the surgical and theatre staff of the Royal South Hants Hospital who have assisted in the collection of tumour samples for steroid receptor assay, and Mrs M. Cross for assistance with data collection.

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Mitogenicity of human fibroblasts in vivo for human breast cancer cells

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Stromal factors have been implicated in the regulation of mammary epithelial cell behaviour, but their influence on human breast cancer is unknown. Fibroblasts were grown in monolayer cell culture from explants of benign and malignant breast tissue and normal skin. MCF7 human breast cancer cells alone (2×10^6 cells) or in combination with live fibroblasts (MCF7+F) were inoculated into the mammary fat pads of 6–8-week-old female nude mice. After 5 weeks tumours were excised, weighed and fixed for histological examination. Addition of live breast fibroblasts significantly increased the retrieval (127/135 versus *52/106, $P<0{\cdot}01$, χ^2 test) and growth (tumour weight 174 ± 11* versus *41 ± 4 mg, mean ± s.e.m., $P<0{\cdot}01$, Mann–Whitney U test) of subsequent tumours. Histological examination did not reveal any morphological difference between the two tumour groups. Injection of fibroblasts alone did not produce tumours. Addition of skin fibroblasts was also stimulatory. Glutaraldehyde-killed fibroblasts increased tumour take but did not stimulate tumour growth. Mononuclear blood leucocytes were ineffective. The results demonstrate that, in this model, fibroblasts exert stimulatory influences on human breast cancer xenograft growth and development.*

Keywords: Breast cancer, fibroblast, tissue culture, nude mice

Breast stroma has traditionally been labelled a mechanically supportive scaffolding for the 'more important' epithelial structures such as ductules. However, there is considerable recent speculation that the stroma plays an active role in determining breast epithelial behaviour[1,2] as in the prostate gland[3]. Little has been published on epithelial–stomal interaction in the breast. Durnberger *et al.*[4] have demonstrated that the dedifferentiation of the mammary epithelial bud in the male fetal rodent occurs in response to a transient secretion of testosterone which does not affect the epithelium directly, but through the mediation of the surrounding fibroblasts. Similarly, Haslam[5] has shown that the response *in vitro* of normal rodent mammary epithelium to the addition of oestrogen is significantly enhanced by the presence of mammary fibroblasts. Durning *et al.*[6] and Azzarone *et al.*[7] working independently have both reported that fibroblasts from patients with breast cancer behave abnormally *in vitro*. This report examines the influence of breast fibroblasts on human breast cancer growth.

Materials and methods

Source of cells

MCF7 human breast carcinoma cells[8] were obtained as a gift from Dr Colby Eton, Tenovus Cancer Research Institute, Cardiff, UK and established in monolayer culture.

Breast fibroblasts were derived from samples of breast tissue obtained from 14 women (mean age 39; range 17–73 years). Samples were taken from macroscopically normal breast (NBF) in three women who had excision of a fibroadenoma and one treated by reduction mammoplasty. The remaining 10 patients had a mastectomy for invasive adenocarcinoma; samples were obtained both from the cancer (TBF) and uninvolved breast (ABF). All macroscopic diagnoses were later confirmed histologically on sections of adjacent tissue.

The breast samples were dissected into 5 mm cubes (approximately) with scalpel blades, discarding excess fat. Ten millilitres of collagenase Type 1A solution 220 units/ml (Sigma Chemical Co., Dorset, UK) was added per gram of breast tissue and the mixture was incubated overnight at 37°C on a blood wheel. The dissociated tisue was centrifuged at 400 *g* for 15 min and an organoid preparation (*Figure 1*) achieved by repeated washing and unit gravity sedimentation as described by Hiratsuka *et al.*[9]. Fibroblast cultures were obtained both from seeding final supernatant cell suspensions and from the cellular outgrowths of organoid explants where they were selectively removed with ethylenediamine tetra-acetic acid according to the method of Owens *et al.*[10]. In later studies, fibroblasts were obtained by standard explant culture of breast tissue segments as benign mammary epithelial cells were no longer required in our laboratory. In these experiments fibroblasts were used when confluent in culture between passage 2 and 6. Skin fibroblasts (SF) were obtained by explant culture of samples from the previously mentioned reduction mammoplasty specimen and from the lower abdomen of a 38-year-old man who underwent herniorrhaphy.

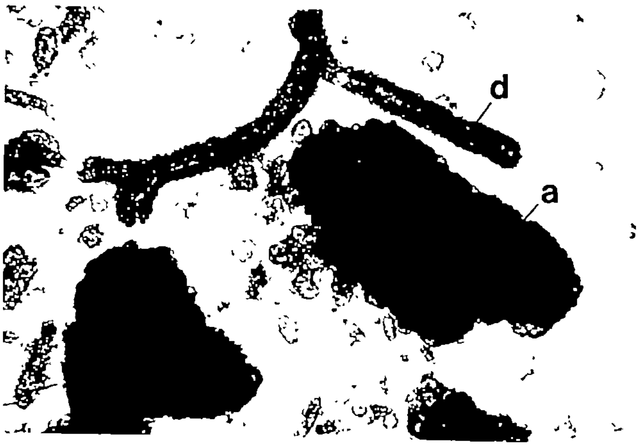

Figure 1 *Organoids viewed under light microscopy × 105. d, Segment of ductule; a, cluster of alveoli and balls of cell*

Monolayer tissue culture

RPMI 1640 culture medium (Gibco Ltd; Paisley, UK) was supplemented with 10 per cent fetal calf serum (Gibco Ltd; Paisley, UK), insulin 0·12 units/ml (Novo Industries, Romford, UK), hydrocortisone 10 μg/ml (Sigma Chemical Co., Dorset, UK), glutamine 4mM (Sigma Chemical Co., Dorset, UK), penicillin 100 units/ml (Glaxo Lab Ltd, Greenford, UK), streptomycin 100 μg/ml (Evans Medical Ltd, Greenford, UK) and amphotericin 2 μg/ml (Squibb, Hounslow, UK). All

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This paper was presented at a meeting of the Surgical Research Society in July 1986 and was awarded the Patey Prize.

tissue culture flasks (Sterilin Ltd, Feltham, UK) were incubated in 5 per cent CO_2 at 37°C in humidified air.

Nude mouse experiments

Athymic nude mice (MF1 nu/nu/OLA) were housed in aseptic conditions at 26°C and received an irradiated diet with acidified water (pH = 4) *ad libitum.*

Two million MCF7 cells or fibroblasts (viability > 95 per cent, trypan blue 0·2 per cent in phosphate buffered saline) were prepared in 50 μl of complete medium and inoculated separately or in combination into the inguinal mammary fat pad. A minimum of six inocula per patient source was used. All mice also received one 2 mg oestradiol pellet (Organon Lab Ltd, Cambridge, UK) subcutaneously on the dorsum at the time of injection. After 5 weeks the mice were killed and inspected for tumour growth. Palpable tumours were dissected free of surrounding stroma, excised, weighed and processed for histology. If no obvious tumour was seen the entire mammary fat pad was excised and fixed for serial histological sectioning. Tumours found only on microscopic examination of the mammary fat pads were arbitrarily awarded a weight of 10 mg.

Killed fibroblasts

Aliquots of fibroblasts in complete medium were treated with 2 per cent glutaraldehyde in balanced salt solution for 90 s and then washed five times to remove any adherent glutaraldehyde. Cell death was confirmed by trypan blue uptake.

Mononuclear leucocytes

Twenty millilitres of heparinized peripheral venous blood were obtained from each of three women who awaited surgery for benign breast disease. A mononuclear leucocyte preparation was achieved by centrifugation of the samples through Ficoll-Paque (Pharmacia Ltd, Milton Keynes, UK) according to the method of Boyum[11]. Aliquots of 2×10^6 cells were suspended in 50 μl of complete medium and investigated for their influence on MCF7 tumour growth in paired experiments.

Results

The addition of breast fibroblasts to MCF7 inocula significantly increased both tumour retrieval and tumour size (*Table 1*). As there was considerable variation in the size of tumour achieved with the combination (*Figure 2*), paired experiments were carried out in 26 mice injecting 2×10^6 MCF7 cells alone into one inguinal mammary fat pad and 2×10^6 MCF7 + 2×10^6 breast fibroblasts into the opposite side. These experiments confirmed the previous findings (*Table 1b*). Morphological examination of both groups of tumours did not reveal any obvious histological difference.

Eight injections of 2×10^6 fibroblasts alone did not form any tumours.

Subdivision of the 'with-fibroblast' tumours did not reveal any significant difference if the fibroblasts were derived from benign or malignant breast tissue (*Table 2*), nor was there any difference in the stimulation achieved between the organoid-derived or supernatant-derived fibroblasts.

Increasing the number of cells in the MCF7 alone inoculum did increase percentage tumour retrieval, but the mean tumour weight remained less than half that of the with-fibroblast group (*Table 3*).

The addition of skin fibroblasts was also stimulatory to MCF7 tumour growth (*Table 4*). The mean tumour weight obtained by the skin fibroblast – MCF7 inoculation was smaller than that achieved by the addition of breast fibroblasts, but the difference was not statistically significant.

Table 1 *Effect of addition of breast fibroblasts (2×10^6 cells) to MCF7 cell inocula (2×10^6 cells)*

	MCF7 alone	MCF7 + breast fibroblasts
(a) Overall results		
Tumours retrieved	52/106	127/135*
Tumour weight (mg) (mean ± s.e.m.)	41 ± 4	174 ± 11†
(b) Paired experiments		
Tumours retrieved	14/26	24/26‡
Tumour weight (mg) (mean ± s.e.m.)	42 ± 6	176 ± 18§

* $P < 0·01$ χ^2 test; † $P < 0·01$ Mann–Whitney *U* test; ‡ $P < 0·05$ χ^2 test; § $P < 0·001$ Wilcoxon paired test

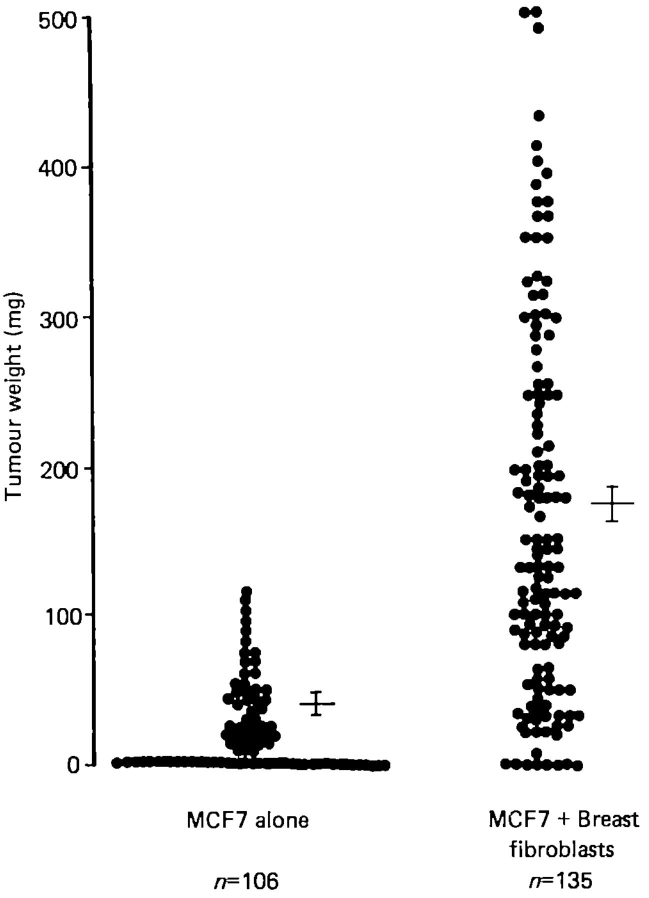

Figure 2 *Effect of the addition of breast fibroblasts (2×10^6 cells) on MCF7 tumour weight (bars show mean ± s.e.m.)*

Table 2 *Effect of different breast fibroblast sources on MCF7 tumour size*

	MCF7 alone (n = 52)	MCF7 + NBF (n = 39)	MCF7 + ABF (n = 54)	MCF7 + TBF (n = 34)
Tumour weight (mg) (mean ± s.e.m.)	41 ± 4[a]	153 ± 15[b]	201 ± 18[c]	157 ± 26[d]

NBF = 'normal' breast fibroblast (see source of cells)
ABF = uninvolved mastectomy fibroblast
TBF = cancerous breast fibroblasts
a *versus* b/c/d, $P < 0·001$; b *versus* c/d, c *versus* d, *P* = n.s. Mann–Whitney *U* test

Table 3 *Effect on tumour weight of increased cell number in the inoculum*

	Inoculum size (cells × 10^6)	Tumour wt (mg) (mean ± s.e.m.)
MCF7 cells alone	2·0 (n = 52)	41 ± 4[a]
	4·0 (n = 17)	73 ± 12[b]
	6·0 (n = 8)	37 ± 13
	8·0 (n = 4)	83 ± 19
MCF7 + breast fibroblasts	2·0 (n = 127)	174 ± 11[c]

a *versus* c, b *versus* c, $P < 0·01$; a *versus* b, $P < 0·05$ Mann–Whitney *U* test

Addition of killed fibroblasts significantly increased tumour retrieval compared with injection of MCF7 cells alone, but there was no increase in tumour size (*Table 5*).

Addition of mononuclear leucocytes (MNL) was not stimulatory to tumour take or growth (tumour weight 50 ± 15 mg *versus* 55 ± 16 mg; MCF7 + MNL *versus* MCF7; mean ± s.e.m. n = 9, *P* = n.s., Wilcoxon paired test).

Table 4 *Effect of addition of skin fibroblasts*

	MCF7 alone	MCF7 + breast fibroblasts	MCF7 + skin fibroblasts
Tumours retrieved	52/106^a	127/135^b	18/19^c
Tumour weight (mg) (mean ± s.e.m.)	41 ± 4^d	174 ± 11^e	139 ± 17^f

a *versus* b, a *versus* c, $P<0{\cdot}01$; b *versus* c, P = n.s. χ^2 test
d *versus* e, d *versus* f, $P<0{\cdot}01$; e *versus* f, P = n.s. Mann–Whitney U test

Table 5 *Effect of addition of glutaraldehyde-killed fibroblasts*

	MCF7 alone	MCF7 + dead fibroblasts
Tumours retrieved	52/106	25/35*
Tumour weight (mg) (mean ± s.e.m.)	41 ± 4	38 ± 4†

* χ^2 test $P<0{\cdot}03$; † Mann Whitney U test $P=0.9$

Discussion

This is the first report of increased MCF7 tumour take and growth secondary to the addition of human breast fibroblasts. The fibroblast-induced stimulation is not caused by a relative increase in the stromal component or sarcomatous change as morphological comparison did not reveal any major difference between the two groups. It is difficult initially to explain the fibroblast effects. The added fibroblasts were not transformed cells as they were used before the seventh passage, did not 'pile up' *in vitro*, had a limited life span and did not produce tumours when injected into nude mice. Transformed fibroblasts may be expected to increase tumour size[12], although at the probable expense of altering the tumour's structural appearance.

The fibroblast source, whether from benign or malignant breast tissue, did not significantly alter the results in contrast to fibroblast migration studies by Durning[6]. Stimulation was achieved in all groups when compared to injection of MCF7 cells alone, although this experimental model is unlikely to discriminate between minor differences in stimulatory potential.

Increased cell density in the with-fibroblast inocula could not account for the observed difference, as doubling cell number to four million in the MCF7 alone category did not produce tumours approaching those obtained by the addition of a similar number of fibroblasts (*Table 3*). This latter finding also indicates that the fibroblast effect is more powerful in increasing MCF7 tumour growth than MCF7 autocrine growth factors which are receiving considerable current attention[13,14].

Normal human skin fibroblasts stimulated growth, thus proving that the fibroblast effect is not specific to breast stromal fibroblasts. Gleiber and Schiffmann[15] have reported that human breast cancer cells secrete a chemoattractant for fibroblasts which would increase the local ratio of fibroblasts to cancer cells. This finding now assumes added significance as non-breast fibroblasts are also stimulatory in our model.

Other normal cells do not possess the stimulatory capacity demonstrated by fibroblasts, as substitution of mononuclear blood leucocytes for fibroblasts failed to achieve increased tumour growth.

The absence of stimulation in the contralateral fat pad inoculated with MCF7 cells in the paired experiments indicates that the fibroblast induced effect is local, not systemic. Xenograft tumour formation and subsequent growth may be the results of two separate biological mechanisms, as killed fibroblasts enhanced retrieval but not growth. Increased MCF7 cell density in the inoculum increased tumour formation, but did not appreciably alter tumour size. It is tempting to suggest that xenograft 'take' is enhanced by a non-specific substratum effect of fibroblasts similar to that caused *in vitro* by fibroblast 'feeder' lines with certain cell types[16,17]. Substantial localized stimulation of tumour growth on the addition of live cells is consistent with the secretion of a fibroblast derived growth factor. Enami *et al.*[18] have proposed a fibroblast derived growth factor secreted by normal rodent mammary fibroblasts which enhanced DNA synthesis of normal rat mammary epithelium *in vitro*. Experimentation with conditioned media from human fibroblast cultures is necessary to elucidate further and isolate fibroblast effects on breast cancer cell growth.

Acknowledgements

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Correspondence

Parotid tumours

Sir,

The article by Maimaris and Ball (*Br J Surg* 1986; **73**: 897) was of interest to all surgeons who treat parotid tumours. I would like to ask what they mean by the statement 'All patients with parotid tumours were traced'. Do they really mean that at the time of writing their paper they were aware of the whereabouts and clinical condition of all 118 patients treated over a 20 year period? If so, I congratulate them, because many are young and geographically mobile and some will have died.

Incomplete follow-up in retrospective studies is a fact of life. I appreciate that in this paper if follow-up was incomplete it would be equally divided between those treated by enucleation or superficial parotidectomy but I cannot take any study of parotid tumours seriously if details of completeness of follow-up are not presented.

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Author's reply

Sir

Mr Hancock is quite right to question the completeness of long term follow-up of any series of patients. Where patients had died death certificate entry was viewed to make sure the cause of death was unrelated. We are fortunate in Mansfield in that the local community is not as mobile as it is in Manchester. Of my parotidectomy cases only one had left the area; this was a patient with adenolymphoma who had a 15 year follow-up to 1981 at which time there was no recurrence. I had not realized before that in the enucleation group there were three patients who had left the area: two of these were pleomorphic adenomas, one with a 2 year follow-up and one with a 7 year follow-up until 1980, and the remaining case was a monomorphic adenoma which only had 1 year's follow-up. I apologize for omitting to record these failures to follow-up; they are, however, a very small number and do not affect the conclusion that conservative parotidectomy is the correct treatment for possible parotid neoplasmas.

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Ruptured azygos vein

Sir

We were interested to read the case report by Sherani *et al.* (*Br J Surg* 1986; **73**: 885) regarding a patient with a torn azygos vein. We have seen two such injuries, both involving unbelted front seat car passengers.

In one the azygos vein was torn off the superior vena cava and in the second the tear was associated with a dissection of the aorta. The azygos vein was easily ligated and the tear in the SVC repaired in the first case. In the second, the aortic dissection was not detected until the characteristic appearances were noted on the surface of the aorta at thoracotomy.

In neither were rib fractures present; it would appear that the mechanism of injury is a stretching of the azygos vein as the thoracic cage is progressively deformed. A tear of the azygos vein is unlikely to escape detection at thoracotomy and is easily managed. We feel it is important to inspect the aorta closely for signs of damage and to search for and secure any posterior mediastinal bleeding points.

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Limited haemorrhoidectomy

Sir

We read with interest the paper by Heald *et al.* describing a new procedure, limited haemorrhoidectomy, for prolapsed thrombosed piles (*Br J Surg* 1986; **73**: 1002), particularly as surgical dogma remains divided between emergency haemorrhoidectomy and conservative management as the treatment of choice[1,2].

In a recent retrospective review in our hospital, 52 of 77 patients admitted with prolapsed thrombosed piles underwent emergency radical haemorrhoidectomy, 96 per cent by registrars and SHOs. The remaining 25 were treated conservatively. Comparing the two treatments, there was little to choose between them. The haemorrhoidectomy group spent significantly longer in hospital (7·9 ± 5·8 days (mean ±s.d.) than the conservative group (4·6 ± 3·6 days) ($P < 0{\cdot}001$, Student's t test), which was in turn longer than that reported by Heald for 20 patients. It will be interesting to see if his short postoperative stay is sustained as the series expands. In our study, complications were slightly more frequent in the conservative group (28 per cent) compared with the haemorrhoidectomy group (15·4 per cent), and at follow-up 3–7 years later the haemorrhoidectomy group had fared marginally better. Our study thus failed to identify the optimal management. Although our results are nor as good as those of Heald, we can say that anal stenosis is not a problem, nor is sepsis.

The treatment of patients with thrombosed piles seems to have been neglected, when one considers the many clinical trials of outpatient and elective procedures. Hopefully this novel approach which combines the two current options in one procedure, i.e. radical surgery for one pile with conservative treatment of the others will stimulate a prospective randomized trial comparing all three.

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1. Dudley HAF. *Hamilton Bailey's Emergency Surgery*. Bristol: John Wright and Sons, 1977:523.
2. Hobsley M. *Pathways in Surgical Management*. London: Edward Arnold, 1979:118.

Antiprotease activity in acute pancreatitis

Sir

I read with interest the recent paper by Goodman *et al.* (*Br J Surg* 1986; **73**: 796–8) on the changes in plasma antiprotease capacity during acute pancreatitis. The authors appear to interpret their data as being inconsistent with the concent of antiprotease consumption during pancreatitis.

It is well established that acute inflammatory disease is associated with a rise in plasma total protease inhibitory capacity (TIC) and that this measurement is of limited clinical application[1]. More important is the relative consumption of specific protease inhibitors, α_2M and antithrombin III whose function cannot be served by the other antiproteases. Previous reports indicate that protease complexes with human α_2M and α_1AT are present in the plasma of patients with acute pancreatitis[2–4]. α_2M–protease complexes can, regardless of the TIC, have profound biochemical[5] and immunological effects[3]. Pancreatitis is not a static model nor is the plasma a fixed space. Large amounts of antiprotease are sequestered in extravascular spaces and the net protease burden to the body may not be adequately reflected in the plasma antiprotease concentrations or TIC.

Whilst it is frequently quoted that α_2M–protease complexes are cleared by the renticulo-endothelial system in several minutes it is important to add that these data were obtained by studying α_2M–trypsin clearance in only four stable healthy individuals. In acute pancreatitis the patient's condition is non-stable, reticulo-endothelial function may be impaired[6] and the predominant protease is not necessarily trypsin[4]. The method used by the authors to detect α_2M–protease complex lacks the sensitivity to quantify small changes in plasma. Because α_2M binds protease non-specifically it is unlikely that reference to a particular protease (e.g. trypsin) will adequately identify all possible α_2M–protease complexes in plasma. The presence of such complexes may be recognized by a reduction in the functional protease binding capacity of α_2M in relation to its concentration measured by immunoprecipitation. The Malmo workers[7] have now adopted this assay technique and confirm earlier reports[3,4] that, following pancreatitis and operative trauma, there can be up to a 20 per cent reduction in the functional capacity per unit weight of α_2M, compared to convalescent values.

Whilst infusion of FFP may not be the ideal treatment for acute pancreatitis, its clinical benefits need not be reflected in a rise of plasma antiprotease concentration. The protease activity of the extravascular space is not easily quantified and it is likely that most of the antiprotease in FFP is sequestered outside the circulation. A considerably greater quantity of human α_2M than that administered may be needed to achieve rapid protease homoeostasis. Unfortunately the volume and sodium content of FFP limit the amount that can be given. A more effective treatment may be to improve α_2M–protease complex clearance (thereby off-loading the renticulo-endothelial system) and to infuse simultaneously an α_2M concentrate from fractionated pooled human plasma[7].

P. K. Donnelly

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1. Shullman NR. Studies on the inhibition of proteolytic enzymes by serum II. Demonstration that separate proteolytic inhibitors exist in serum: their distinctive properties and specificity of action. *J Exp Med* 1952; **95**: 593–603.
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Fibrin adhesive in small bowel anastomoses

Sir
We read with interest the paper by Hjortrup *et al.* (*Br J Surg* 1986; **73**: 760–1) on the use of fibrin adhesive in small bowel anastomoses.

While a bursting pressure technique may be an appropriate test of an anastomosis' ability to resist physiological stresses, it is a poor method of measuring, or comparing, the true strength of intestinal wounds[1]. The tension placed upon an intestinal anastomosis is proportional to the intraluminal pressure and the radius of the viscus, as stated in Laplace's law[2]. When using a bursting pressure method to assess the strength of intestinal wounds, a 7-day-old anastomosis, with its reduced compliance and radius, will often appear to be stronger than the normal bowel[3,4]. Breaking strength measurements[3], or calculation of wall tension at rupture[2], demonstrate that this is not the case.

Since the anastomoses represented the site of rupture in very few of the specimens tested in this report, comparisons of anastomotic strength cannot be made. While we agree that fibrin adhesive may permit a safe anastomosis, the authors' conclusion that fibrin adhesive anastomoses are equal in strength to sutured anastomoses is not substantiated by the experimental data presented.

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1. Hastings JC, Van Winkle W, Barker E, Hines D, Nichols W. Effect of suture materials on healing wounds of the stomach and colon. *Surg Gynecol Obstet* 1975; **140**: 701–7.
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Author's reply

Dear Sir
We agree with the arguments of the above, and would like to point out that we concluded in the report itself that: the bursting strength of *the bowel segments* with fibrin adhesive anastomoses, in our experiment, was similar to that of *segments* with sutured anastomosis.

In the summary this was shortened to: 'There was no significant difference in the *in vivo* bursting strength after 7 days'.

A. Hjortrup

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Aorto-enteric fistulae

Sir
We read with interest the article by Thomas and Baird (*Br J Surg* 1986; **73**: 875–8) on the conservative approach to the operative correction of secondary fistulae. We wish to support conservative surgery and the avoidance of extra-anatomic bypass in primary aorto-enteric fistula. A 59-year-old man with a spontaneous fistula between a 4 cm aneurysm and the third part of the duodenum was managed by primary closure of the duodenum and Dacron tube graft to the aorta. This patient is without complication at a follow-up of 12 months.

If contamination is minimal the simplest surgical procedure should be used.

S. G. Chiverton
P. M. Perry

Queen Alexandra Hospital
Cosham
Portsmouth
Hampshire

Breast lumps and seat belt injury

Sir
The recent report from Professor Taylor's unit in Southampton regarding the coincidental association between seat belt trauma and carcinoma of the breast bears particular significance to a case recently encountered on our unit (*Br J Surg* 1986; **73**: 106–7).

A 61-year old woman had been a front seat passenger involved in a road traffic accident six weeks before her presentation. The injuries sustained included extensive bruising from the left shoulder to the umbilicus. Subsequent examination of the traumatized left breast resulted in the discovery of numerous breast lymps. A close associate of the patient, who was familiar with the above report, recommended that she be further investigated.

On examination, 6 weeks after the accident, there was still some visible bruising. Five separate discrete lumps were palpable in the affected breast. Four of these were described as clinically benign, the fifth, the largest, showed some degree of deep fixity. Mammography revealed changes strongly suggestive of carcinoma and excisional biopsy of the suspicious lesion confirmed the presence of an infiltrating intraduct carcinoma.

This case not only further illustrates the attention that seat belt trauma seems to draw to breast lumps, as pointed out by the six cases of solitary breast lumps from Southampton, but also underlines that even the presence of multiple lumps, shortly after trauma, should not deter the clinician from thorough investigation to exclude neoplasia.

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Book reviews

Management of Back Pain

R. W. Porter. 255 × 190 mm. Pp. 183. Illustrated, 1986. Edinburgh: Churchill Livingstone. £25.00.

Back pain is a highly readable book, which is interesting throughout, and is sustained by the author's enthusiasm. My criticisms are minor irritations which do not detract from what is overall an excellent book. For example, too many case histories for each condition are given and the chapters on pain are separated whereas they naturally go together. It is also irritating to find symphysis misspelt in consecutive sentences, including the phrase 'public symphysis'. The book aims to stimulate interest rather than provide a definitive text and in this it succeeds The basic sciences are well covered and include unusual but exciting facts such as the possible significance of birth injury in the aetiology of pars defects. The sections on investigations are adequate although magnetic resonance imaging is, perhaps understandably, only briefly mentioned. It would be valuable to have more on alternative treatment. The hostility of the medical profession is sometimes based on ignorance and we may be better placed to advise patients if books such as this told us something about these practitioners. Otherwise I have no hesitation in recommending this as a book which will stimulate what may be your fading interest in back pain.

D. M. Hunt

Farquharson's Textbook of Operative Survery. Seventh edition

R. F. Rintoul. 250 × 190 mm. Pp. 658. Illustrated. 1986. Edinburgh: Churchill Livingstone. £45.00.

Farquharson is a popular textbook of operative surgery which has served generations of FRCS candidates well. A new edition has been long awaited and here it is, impressively presented; with small chapters which are easy to read and assimilate; above all there are new authors who add authority and lustre to the work. Although the 'feel' of a one author work has been lost with these innovations I welcome this new edition and wish it and its readers well.

Although my overview of the book is complimentary there are some curious omissions of newer surgical techniques and, likewise, there are some curious inclusions of outdated, indeed primitive, methods. Some important controversies in operative surgery are not addressed adequately and in places the writing still has an old world charm rather out of keeping with the styles of some of the newer authors.

As inclusions of the outdated, the photograph of a colostomy with glass rod and rubber tube bridge, with delayed opening 'covered' by a tube caecostomy, on page 433 made my heart sink. The picture of venesection on page 54 with rubber tubing as a tourniquet is also an unfortunate holdover from the past.

The use of a buried strip of skin to repair an inguinal hernia surely has no place in this era of synthetic sutures? The choice of treatment in thyrotoxicosis, the drugs *versus* surgery argument, the role of radioactive iodine and the preparation of the patient for surgery are not the distillation of the best modern practice which I would expect to read.

Other omissions include sutures and their properties; choices and safeguards using local anaesthesia; the microbiology of skin grafting and the role of β-haemolytic streptococci in split skin graft failure; splenic conservation and postsplenectomy management; myocutaneous flaps; microvascular surgery; endoscopic sympathectomy for upper limb hyperhidrosis and pigtail ureteric catheters.

The descriptions given of the operative technique for varicose vein stripping and inguinal herniotomy in infancy are both controversial and may cause examination candidates difficulty. Many examiners opine that stripping the long saphenous vein downwards from groin to leg causes fewer problems with the saphenous nerve. Similarly, most of my colleagues and the literature suggest that mobilizing the cord and testicle into and through the groin wound in childhood inguinal herniotomy is more hazardous than *in situ* groin herniotomy. The hazard is alleged to be to the testicular blood supply, more ischaemic damage being reported when full scale scrotal content mobilization is employed.

These are detailed criticisms; the book will be judged as a whole by its readers, it will fulfil the needs of FRCS candidates and will become an important reference work for the current generation of trainees who pass the exam and return to hospitals where large libraries are not immediately available.

H. B. Devlin

Cunningham's Manual of Practical Antomy. Volume 1: Upper and Lower Limbs

G. J. Romanes. 275 × 175 mm. Pp. 263. Illustrated. 1986. Oxford: Oxford University Press. £8.50.

Cunningham's Manual of Practical Anatomy. Volume 2: Thorax and Abdomen

G. J. Romanes. 275 × 175 mm. Pp. 298. Illustrated. 1986. Oxford: Oxford University Press. £8.50.

Cunningham's Manual of Practical Anatomy. Volume 3: Head, Neck and Brain

G. J Romanes. 275 × 175 mm. Pp. 346. Illustrated. 1986. Oxford: Oxford University Press. £8.95.

Professor Romanes is to be congratulated on the brightened 'new look' Manuals of Practical Anatomy. The 14th edition of Cunningham's Dissection Guides have been expanded, enlarged and improved to act as a dissection guide and (like Gaul) a textbook in three parts. All volumes have been enlarged by an inch or so and the typeface made much clearer with the dissection portions highlighted in radiant blue. Most of the original artwork has been retained, making this trio a wealth of information slightly overpowering to the undergraduate but first rate for the primary FRCS student.

In volume 1, there are some useful additions including numerous high quality radiographs and some poor quality surface anatomy plates. In volume 2, the author is to be congratulated on including a very compact and readable account of development, supplemented by first rate diagrams; many however are reproduced too small for easy interpretation. Another innovation is the addition of 15 pages of CT scans and transverse sections most clearly illustrated. My only sadness was that the most commonly seen CXR on page 10 was the worst produced plate of the three volumes.

Volume 3 has the usual head and neck anatomy plates with the added interest of CT scans, though more NMR would have helped the otherwise excellent brain sections. Again at the end of this volume is a short transverse section and CT atlas as well as an easy to read developmental chapter.

After nearly a hundred years and 15 editions, Professor Romanes has once again updated, modernized and improved this already popular text. Any primary FRCS student would be well advised to have a look at the three volumes and use them as a single composite textbook of anatomy for the primary FRCS.

P. Abrahams

Principles, Techniques and Applications in Microsurgery

T. S. Chang. 260 × 180 mm. Pp. 387 + ix. Illustrated. 1986. Chichester: John Wiley and Sons Ltd. £85.45.

This is an excellent and comprehensive review of microsurgery as practised by the foremost microsurgeons in China. It has been translated for publication in the West by P. C. Leung who writes a disarming note explaining that this is his first translation, undertaken because of the excellence of the book in its original Chinese. His success results in a text clear and easy to read. The translation should not then deter the reader. This is, indeed, a 'good read'. The book is well produced with clear and relevant black and white illustrations. For those searching an introduction to the basic principles, the opening chapters cover these very clearly, commencing with an historical review. The remainder covers every aspect and area in which microsurgery is carried out, literally from head (extracranial/intracranial bypass) to foot (toe transplantation).

This is very much the Chinese experience and has a fascination in revealing information from an area recently unknown. It presents us with the work of Chinese surgeons of the most advanced ability, who have been involved in microtechniques from the outset and are now keen to be represented in the West. There are many astonishing case reports, but no complete series are given, unless they are represented in the section of the bibliography in Chinese.

This is an interesting and useful textbook for reference for all those undertaking microsurgery. Perhaps it will be followed by more Chinese revelations in other areas of surgery.

J. M. F. Clarke

Hamilton Bailey's Demonstrations of Physical Signs in Clinical Surgery. 17th edition

A. Clain. 230 × 150 mm. Pp. 622 + xiv. Illustrated. 1986. Bristol: John Wright and Sons. £17.50.

The latest edition of this 'classic surgical companion' is an excellent advert for the surgical discipline. It is concise, interesting, well presented and pithily written. These factors will keep this book as a firm favourite with medical students as well as providing an instant revision course for FRCS candidates.

Allan Clain has thoroughly revised the text and updated many of the comments about the interpretation of the signs. Whilst the scientific aspects of surgical diagnosis are mentioned, the thrust of the book is to support the unchanging value of a full history and examination.

The historical footnotes remain a feature of this book, which spans all general surgical interests, gynaecology and orthopaedics.

There are two criticisms. First, it is enlarging with each edition and, with more than a quarter of it devoted to orthopaedics, the content might be trimmed thus holding the price to a level which would encourage students to purchase it. Secondly, detail is lost in some of the reproductions of the black and white photographs, which renders them unhelpful.

This is a thoroughly reliable and fascinating book, which should be available to all medical students and fellowship candidates.

J. A. Rennie

Current Orthopaedics. Volume 1

R. A. Dickson. 295 × 210 mm. Pp. 131. Illustrated. 1986. Edinburgh: Churchill Livingstone. £60.00. Quarterly

This is a new journal which presents in each number a collection of review articles. Each issue focuses on a specific topic discussed in the form of a mini symposium. The Editor hopes that this review journal will cover a core postgraduate syllabus in every four year cycle, thus differentiating it from the other orthopaedic journals, which usually cover their 'review' subject in much greater length. The essence of the journal will be contributions, of not more than 5000 words each, in particular topics with 10–25 key references.

In addition to the mini symposium each number will contain articles covering basic science, a historical review, general medicine, children or adults, trauma and imaging. The first mini symposium was on 'failed joint replacement' and apparently the mini symposium in the second number will be on 'soft tissue injuries of the knee'.

The concept of this new journal is an interesting one. Whether it will succeed will depend on the editor's ability to fulfil his aims and present a core postgraduate syllabus every 4 years. The reviewer wishes him well in this endeavour.

C. Galasko

Operative Techniques in Arterial Surgery

A. S. Ward and J. M. Cormier. 190 × 250 mm. Pp. 412 + xiv. Illustrated. 1986. Lancaster: MTP Press Ltd. £95.00.

Unlike most contemporary vascular surgical textbooks of this size which are written by a number of contributors selected for their expertise in special areas, this volume was written and edited by only two authors, one English and one French. This has resulted in a variety of opinion being replaced by a uniformity of approach to this specialty which makes attractive reading for the beginner in vascular surgery, although the more experienced may inevitably find certain controversial aspects treated rather dogmatically.

The whole spectrum of arterial surgery is well covered and the chapters on trauma and percutaneous transluminal angioplasty are especially welcome. While this is essentially a book on operative technique, a wider view of vascular disease in general and pre-operative assessment and preparation in particular is included. The text, which is well presented, clear and straightforward to read, is backed up by excellent and up-to-date selected references at the end of each chapter. In addition, a very real strength of the volume is found in the many superb line drawings of operative situations which are available among its pages.

This textbook is an excellent read for vascular surgeons in training and even the established surgeon will find much of interest. Nevertheless, at £95 it is an expensive buy for the individual, although it can certainly be recommended as a very worthwhile purchase for departmental libraries.

J. Murie

Radiotherapy in Clinical Practice

H. F. Hope-Stone. 250 × 190 mm. Pp. 454. Illustrated. 1986. London: Butterworths. £45.00.

Until relatively recently the trainee radiotherapist despaired at the lack of good text books dealing authoritatively with the radiotherapeutic treatment of malignant disease. On both sides of the Atlantic there are now excellent tomes dealing with both the art and the science of the subject. This 450 page multi-author hard-backed book will become the firm favourite for many. The fifteen authors include a radiographer, a physicist and a medical oncologist. Dr Hope-Stone's choice of contributors includes several colleagues at the London Hospital although there is a reasonable geographical scattering but only from the British Isles. The format of the book is attractive with good line drawings; however, it is unfortunate that the X-ray reproduction is not of such quality to allow appreciation of fine radiological details of, for example, Ewing's Sarcoma or metastases in the chest. The emphasis of the book is on detailed technical radiotherapeutic practice as it affects the management of patients with malignant disease. As the clinical practice of radiotherapy is so intimately involved with chemotherapy it is difficult, particularly in the chapter on paediatric tumours, to deal with one aspect in detail without the other.

There is no attempt to give more than a broad outline of concomitant chemotherapy. Some minor omissions such as dose details for treating oesophageal cancer, radiation protection structure and concept of radiotherapeutic requirements of a population are inevitable. The recent expansion of knowledge and interest in Kaposi's sarcoma is not adequately covered. However, there are very few criticisms of this excellent book. The chapter on the treatment of benign conditions is refreshing, showing it as neither antique nor inappropriate. Gynaecological malignancies are covered in a detailed and authoritative if partisan manner. The book is very modestly priced at £45 and I am sure it will soon find itself on the bookshelves of all students of radiotherapy and oncology—a very welcome statement of British practice which is second to none in radiotherapy.

Margaret Spittle

Oxford Textbook of Functional Anatomy. Volume 1

Pamela MacKinnon and John Morris. 275 × 220 mm. Pp. 128. Illustrated. 1986. Oxford: Oxford University Press. £10.95.

This book, ultimately to appear as three volumes, with volume 2, *Thorax and Abdomen* and volume 3, *Head and Neck* in preparation, is aimed at the medical undergraduate rather than the aspiring surgeon. A systematic approach is taken using a limited text, abundant drawings, excellent radiographs and clinical cases; surface and functional anatomy is emphasized throughout. Each system is tackled as a seminar requiring 2–3 h of study. The text contains dissection notes and also includes questions designed to monitor progress. The factual information is purposefully limited so as not to overload the hard-pressed preclinical medical student of today.

The limitations of this book for the young surgeon, looking for a text for the primary FRCS examination, is the absence of a description of regional interrelationships so necessary for surgical dissections. Thus, each muscle, nerve and vessel is illustrated separately which is a refreshing way of clarifying muscular insertions and origins, for example, or the disposition of branches of nerves and vessels, but doesn't give the surgeon much confidence in identifying structures exposed during operations on the wrist, cubital fossa, axilla, etc. The regional approach is not compensated for by the dissection notes since these appear to be largely perfunctory. My personal view is that the combination of dissection notes with readable text is unworkable. At the dissecting table insufficient instruction is given to complete the work unaided; and the atmosphere of a dissecting room is not condusive to reading long screeds of text. At home, or in the library, the reader is distracted, not only by a text interposed with dissection instructions, but also by the acrid smell of body fat which inevitably impregnates the pages.

This first addition has a confusing diagram, showing the changes in the axis of rotation of the shaft of the femur, after fracture of the neck illustrated by using a composite diagram of an AP view of the hip joint and a vertical view of the upper end of the femur. The red pointers on some diagrams are often difficult to follow whilst duplication of at least one illustration seems unnecessary.

M. Berry

Notices and announcements

Meetings

27 March 1987
Angioplasty in Surgical Practice
Edinburgh, UK
Information: Mrs Lynda McDonald, Ninewells Hospital and Medical School, Dundee DD2 1UB, UK

28 March–4 April 1987
Fifth Cardiosurgical Symposium
Zürs, Austria
Information: Professor M. Deutsch, II. Chirurg. Univ.-Klinik Wien, Spitalgasse 23, A-1090 Vienna, Austria

1–3 April 1987
Association of Surgeons of Great Britain and Ireland
Liverpool, UK
Information: Mr B. T. Jackson, Association of Surgeons of Great Britain and Ireland, Royal College of Surgeons, 35/43 Lincoln's Inn Fields, London WC2A 3PN, UK

5–10 April 1987
American Society of Colon and Rectal Surgeons Annual Convention
Washington, DC, USA
Information: Miss H. Gibson, 615 Griswold, 1717 Detroit, MI 48226, USA

6–8 April 1987
Annual Meeting of the American Association for Thoracic Surgery
Chicago, Illinois, USA
Information: American Association for Thoracic Surgery, 13 Elm Street, Manchester, MA 01944, USA

27–28 April 1987
International Symposium on Reoperative Infrarenal Arterial Surgery
Rigshospitalet, State University Hospital, Copenhagen, Denmark
Information: International Symposium on Reoperative Infrarenal Arterial Surgery, Department of Surgery D, Section of Vascular Surgery, Rigshospitalet, State University Hospital, 9 Blegdamsvej, DK-2100 Copenhagen Ø, Denmark

28–30 April 1987
Annual Meeting of The American Laryngological, Rhinological and Otological Society
Denver, Colorado, USA
Information: Dr Roger Boles, President, c/o Lilibet Coe, Administrative Assistant, Kutztown Road, East Greenville, PA 18041, USA

9–15 May 1987
Digestive Disease Week of the American Gastroenterological Association
Chicago, Illinois, USA
Information: Registration Supervisor, Slack Inc., 8900 Grove Road, Thorofare, NJ 08086, USA

10–13 May 1987
Joint Annual Meeting of the American Lung Association, the American Thoracic Society and the Congress of Lung Association Staff
New Orleans, Louisiana, USA
Information: American Thoracic Society, 1740 Broadway, New York, NY 10019, USA

10–13 May 1987
XXII Congress of the European Society for Surgical Research
Aarhus, Denmark
Information: Aarhus Turistforenings Kongresbureau (Convention Bureau), Radhuset, DK-8000 Aarhus C, Denmark

15–16 May 1987
Fifth International Nijmegen Vascular Symposium on 'Angioplasty—Vascular Surgery—Combined Approach'
Nijmegen, The Netherlands
Information: Dr S. H. Skotnicki, St. Radboud Hospital, PO Box 9101, 6500 HB Nijmegen, The Netherlands

20–23 May 1987
78th Annual Meeting of the American Association for Cancer Research
Atlanta, Georgia, USA
Information: Margaret Foti, American Association for Cancer Research Inc., Temple University School of Medicine, West Building, Room 301, Broad and Tioga Streets, Philadelphia, PA 19140, USA

22 May 1987
British Association of Endocrine Surgeons
Edinburgh, UK
Information: Mr A. W. Goode, Honorary Secretary to the British Association of Endocrine Surgeons, Surgical Unit, The London Hospital, Whitechapel, London E1 1BB, UK

24–30 May 1987
Annual General and Scientific Meeting of the Oto-laryngological Society of Australia
Surfers Paradise, Queensland, Australia
Information: OLSA Meeting Secretariat, PO Box 731, Toowong Q4066, Australia

6–7 June 1987
Course on the Applied Surgical Anatomy and Operative Surgey of the Liver, American Association of Clinical Anatomists
Toronto, Canada
Information: Dr R. Ger, Winthrop University Hospital, Mineola, NY 11501, USA

10–12 June 1987
69th Meeting of the Endocrine Society
Indianapolis, Indiana, USA
Information: The Endocrine Society, Annual Meeting Office, 428 E Preston Street, Baltimore, MD 21202, USA

15–19 June 1987
Advanced Hepato-Pancreatico-Biliary Surgery
Lund, Sweden
Information: Professor S. Bengmark, Box 5121, S-220 05 Lund 5, Sweden

22–26 June 1987
Peritoneum and Peritoneal Access
Lund, Sweden
Information: Professor S. Bengmark, Professor of Surgery, Box 5121, S-220 05 Lund 5, Sweden

24–28 June 1987
Annual Meeting of the Western Thoracic Surgical Association
Colorado Springs, USA
Information: Western Thoracic Surgical Association, 13 Elm Street, Manchester, MA 01944, USA

7–8 July 1987
Blood Flow '87 (Biological Engineering Society – Blood Flow Group)
University of Leeds, UK
Information: Mr R. Price, Department of Medical Physics, Leeds General Infirmary, Leeds LS1 3EX, UK

9–11 July 1987
XIIth International Update on Liver Disease
London, UK
Information: Professor Neil McIntyre, Academic Department of Medicine, Royal Free Hospital, Pond Street, London NW3 2QG, UK

31 August–4 September 1987
Surgical Efficiency and Economy
Lund, Sweden
Information: Professor S. Bengmark-SEE, Box 5121, S-220 05 Lund 5, Sweden

9–11 September 1987
Clinical Controversies in Inflammatory Bowel Diseases
Bologna, Italy
Information: Organizing Secretariat, SO.GE.PA.CO. Spa. piazza Constituzione, 5/c, 40128, Bologna, Italy

15–18 September 1987
The British Society of Gastroenterology Jubilee Meeting
London, UK
Information: The Administrative Secretary, The British Society of Gastroenterology, 3 St Andrew's Place, Regent's Park, London NW1 4LB, UK

Leading articles

Br. J. Surg. 1987, Vol. 74, April, 235–236

Impact of new technology on anorectal disorders

For many years the anorectum was a forbidden area for both the physiologist and clinical scientist. Few ventured near, and as a consequence the region has been slow to reveal its secrets. The early pioneers spent most of their time inserting pressure probes of various designs into the anal orifice. Arguments raged over whether balloons, perfused tubes or strain gauges were the optimum instruments for measurement. Although a considerable amount of data was generated, it was difficult to interpret. Gradually, these intrepid pioneers became bolder and attacked their unfortunate subjects with concentric EMG needle electrodes. However, the information obtained was still relatively crude, and investigation remained confined to a handful of committed, yet often outstanding enthusiasts. Over the last 10 years, this situation has changed dramatically with an explosion in information related to the anorectum and its pathophysiology. The crude manometric and EMG measurements have led the way to more sophisticated techniques which utilize microtransducers, telemetry capsules and single fibre EMG needles. There has been greater emphasis on dynamic and simultaneous measurement rather than static, isolated investigation. It is now possible to measure anorectal pressure and electrophysiological activity in the sphincter while simultaneously visualizing the anorectum radiologically[1,2]. The use of hair-like wire electrodes have converted electrophysiological investigation from an uncomfortable procedure into a relatively painless one, and this has made investigation more physiological than hitherto. Such dynamic measurement of anorectal function is rapidly emerging from a research technique into a service requirement.

Much of the information generated has real practical value. Most observers will be aware that Parks and his colleagues established with reasonable certainty that idiopathic faecal incontinence was due to denervation of the anal sphincter[3]. Few, however, will have realized that patients with perineal descent, yet who are continent, have evidence of denervation of the sphincter[4] and are at considerable risk of being rendered incontinent by quite minor, local procedures. Using the new dynamic technology, the cause of certain types of severe constipation seen in young women has gradually been unravelled. Colonic transit studies have shown that a significant proportion of these patients pass the contents of their colon from the ileocaecal junction to the rectum at a normal rate. The hold-up is in the rectum; combined proctography and EMG measurements have confirmed the initial suspicion[5] that the problem is due to an inappropriate contraction of the puborectalis muscle during attempted voiding[1]. It seems wise to identify this group of patients so that appropriate management can be instituted. If surgery is required, partial colectomy may fail. Unfortunately, direct attacks designed to alleviate this contraction by division of the muscle have been disappointing[6]. Whether biofeedback will be more successful remains to be determined. Radiological abnormalities are also frequently seen in this group of constipated patients. These include recto-anal intussusception, rectocoele and anterior rectal wall prolapse. It is not known whether these visual abnormalities are the cause or the effect of the symptoms, but attempts to correct them surgically have infrequently relieved the constipation[7].

There is more optimism in the treatment of the solitary rectal ulcer syndrome, a condition which has defied explanation since it was first described more than 100 years ago[8]. Proctography in patients with this problem demonstrates that the rectal wall invariably prolapses into the anal canal on straining[9]. Simultaneous pressure recordings have also shown[10] that the ulceration occurs when intrarectal pressure is high. These findings probably explain why the syndrome is prevalent in young people and disappears with age. The ulceration only occurs when there is a combination of prolapse and raised intrarectal pressure[1]. The puborectalis and external anal sphincter become weaker with age as fibrosis and denervation occur, hence the high pressures generated at a younger age are reduced, the patient defaecates more easily and the ulcer heals. It is becoming clear that the ulcers will heal if the prolapse can be adequately fixed, but it is unlikely that all symptoms will disappear if the associated puborectalis spasm remains. Selection of patients by dynamic investigation seems to be an essential part of management in this previously intractable disease. Voiding studies have also demanded some re-thinking with regard to the terminology used to classify rectal prolapse. As mentioned above, not all rectal prolapses appear at the anus; some

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remain intra-anal and are occult rather than overt. It is also difficult at this time to be sure that all prolapses are not really intussusceptions.

What does the future hold? There is no doubt that improvements in technology are required. Simplification of the hardware should make it more compact and mobile. More data are required in normal subjects and particularly in the younger age group. Unfortunately, such information is difficult to obtain because of ethical constraints related to the radiation dose. It is also unlikely that the same degree of visual definition can be achieved with alternative imaging techniques. Despite these drawbacks, the new technology opens the door to the understanding of such sophisticated mechanisms as those responsible for continence[11], for the differentiation of flatus from solid[2], the interaction between micturition and defaecation, and the co-ordination of colonic function with that of the anorectum. Such basic information should help to explain problems encountered after surgical procedures such as low anterior resection and pelvic pouch construction. Perhaps insight will be gained into previously ignored problems such as proctalgia fugax and other non-specific types of anorectal pain. It is clear that the surgeon who takes an interest in disorders of continence and defaecation is becoming highly specialized. He needs sophisticated tools to understand and treat his patients. Some of these are now available and in the future will no doubt be refined. Even now, these techniques are demonstrating pathophysiological abnormalities in patients who were often considered to have supratentorial problems. It would be a foolish clinician who nowadays labelled his patient with odd anorectal symptoms as having a psychiatric disorder without first performing more sophisticated investigations.

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Surgical treatment of hydatid disease of the liver

Hydatid cysts of the human liver occur when man becomes an accidental intermediate host for the larval form of *Ecchinococcus granulosus*, which lives as an adult worm in the canine intestine. Hydatid disease is endemic in countries around the Mediterranean, Australia and South America, as well as in a few areas in North America and the UK. The disease is usually acquired by children in rural communities who live in association with sheep and dogs. However, as a result of the ease of travel and migration, the disease is now being encountered in immigrant adults in many parts of the world in which it is not endemic[1,2]. The liver is the most common site infected in the adult. About one-third of patients with liver hydatid cysts have other sites involved, including peritoneum, lungs, spleen, brain and bone.

The liver cyst consists of a layer of dense host fibrous tissue (pericyst) and the parasite itself contributes an external laminated membrane and an inner thin germinal layer. This latter layer forms capsules and scolices which may become detached into the cyst fluid. It also may develop infoldings that become daughter cysts. Even very large cysts may be asymptomatic. Pain may result from stretching of the liver capsule or leakage of contents. Leakage may also produce urticaria or anaphylaxis when cyst fluid is absorbed into the blood stream. An expanding cyst may erode into the biliary tract leading to infection of the cyst cavity, or may drain its contents including daughter cysts into the bile duct producing obstructive jaundice, with or without cholangitis. This important complication of intrabiliary rupture is discussed at length by Alper *et al.* in this issue of the journal.

The diagnosis of hydatid disease of the liver is usually easily made when a liver cyst is found in a patient from an endemic area. Calcification of the cyst wall is commonly seen on plain X-ray films. Ultrasound or CT scanning may show the characteristic picture of a cyst containing multiple daughter cysts. Serological studies also provide useful verification. Both the Casoni skin test and the indirect haemagglutination test are positive in about 85 per cent of patients, but the latter is more specific for hydatid disease.

Medical treatment is not curative at present. Mebendazole has been reported to have scolicidal effects *in vitro*, and has produced some symptomatic and objective responses in patients, but the results are not reliable. A newer drug, albendazole, also has scolicidal effects, and may be more effective than mebendazole, although hepatotoxicity has been observed. These drugs should not be used as primary treatment, but may be helpful in patients in whom surgery is contra-indicated, or when there has been spill of live scolices or daughter cysts[3].

Although most authors agree that the primary treatment of hydatid cyst of the liver is surgical, there is considerable controversy regarding the place of cyst aspiration, the choice between resection and evacuation, and the management of the residual cavity, including the use of scolicidal agents and the advisability of external drainage.

Cyst aspiration

Because the cyst fluid is usually under pressure, percutaneous puncture for diagnostic purposes is to be avoided as it allows leakage into the peritoneal cavity and anaphylaxis. Some authors have suggested intra-operative puncture to aspirate fluid for diagnosis and allow installation of scolicidal material before definitive surgical management. This technique may be effective in young patients with simple cysts, but is not practical in the usual adult patient whose cyst is filled with myriad daughter and grand-daughter cysts. However, the technique is safe, as long as adequate care is taken to avoid spill into the peritoneal cavity, and non-toxic scolicidal agents are used.

Resection or cyst evaluation

Complete surgical removal is the ideal treatment of the disease, and can be accomplished by removal of all germinal lining, daughter cysts, fluid and scolices leaving the pericyst; or by resection of the intact cyst including pericyst. Because of the

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risk of spillage of infective material into the peritoneal cavity leading to recurrent disease, some authors have favoured resection[4,5], but this approach carries a significant operative risk and is not applicable in many cases.

We and others[1,6] have found that with meticulous protection of the peritoneal cavity and pleura, complete evacuation of the cyst cavity can be accomplished leaving only the pericyst-lined cavity, and that the incidence of recurrent hydatid disease is extremely low. We reserve resection for the few cysts that are peripherally placed so that excision involves transection of only a small amount of liver tissue and does not damage major ducts or vessels.

Management of the residual cavity

A variety of techniques have been proposed to deal with the residual cavity after evacuation. The use of scolicidal agents to sterilize the cavity has merit, but formalin, the original scolicidal agent, has been shown by many authors to be highly dangerous, producing death from acidosis[7] and from obliterative cholangitis. Formalin is absolutely contra-indicated in the treatment of hydatid disease. Hypertonic saline (15–20 per cent) or cetrimide are acceptable agents with which the cavity should be filled for at least 10 min after evacuation of contents.

Thereafter, uncomplicated cysts which do not communicate with the biliary tract and are uninfected may be simply filled with normal saline and closed without drainage if they are deep in the liver. Very superficial cysts may be unroofed back to liver tissue so that the remaining space is left open in the peritoneal cavity. There seems little advantage in techniques such as omental packing to obliterate these cavities, as infection is quite uncommon.

In complicated cysts, there is more concern regarding infection, and drainage of the residual cavity is recommended. Where communication with the biliary tract is found, attempts should be made to directly close the fistula with fine sutures. Short term closed system drainage is then adequate. For frankly infected hydatid cysts, the cavity should be treated like a liver abscess after evacuation of cyst material, with insertion of an adequate diameter open drain. Routine exploration of the common duct should not be carried out in patients with biliary communication, but should be reserved for those who have been shown pre-operatively to have cyst material in the biliary system.

The results of this conservative approach are excellent, with low morbidity and very low operative mortality. Our own experience includes 60 patients treated since 1967, 57 of them by surgery. There have been no operative deaths and we have had only four recurrences of which three were known to have hydatid disease which could not be completely removed at the time of the first procedure.

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Non-specific abdominal pain as a cause of acute admission to hospital

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Pain localized to the abdomen is a feature of many diseases and the definition of patterns of pain associated with specific diagnoses was a major achievement of clinicians in the 18th and 19th centuries. Such has been the success of this approach that the new medical student could be forgiven for thinking that patients with abdominal pain only require a careful history, examination and a few well chosen investigations before a diagnostic label can be applied and appropriate treatment given. It is disappointing to find that this logical progression is frequently unsuccessful in pointing to either diagnosis or treatment. General practitioners are well aware that many patients suffer from episodes of abdominal pain to which no label can be firmly attached, and a recent study showed that only 9 (6 per cent) of 150 patients presenting to an urban teaching practice with abdominal pain were referred to hospital as emergencies[1].

More surprisingly, a large number of patients attending hospital as an emergency with abdominal pain also have no definite diagnosis made. Only recently has the size of this problem been documented. Ingram and Evans noted that 26 per cent of women admitted to hospital with right iliac fossa pain were eventually discharged without a diagnosis[2] and Winsey and Jones described the same outcome in 37 per cent of children admitted to hospital with abdominal pain[3]. The Oxford record linkage study[4] found undiagnosed abdominal pain to be the sixth most common cause of hospital admission in females and the tenth most common cause of admission in males. Wilson *et al.*, in a study of 1196 patients attending Leeds General Infirmary as an emergency with abdominal pain[5], reported that no diagnosis was made in 45·6 per cent of patients, 30 per cent of whom were admitted to hospital. A subsequent multicentre study in Britain of 6097 patients found that 43 per cent of those attending with acute abdominal pain eventually had no diagnosis made[6]. These published figures are consistent with the clinical experience of district general hospitals, and a 'diagnosis' of non-specific abdominal pain (NSAP) is common.

Few studies have followed up patients with NSAP to try to discover the natural history of the condition. A comprehensive study by Jess *et al.*[7], in Copenhagen, of 730 patients admitted to hospital with a diagnosis of acute abdominal pain, revealed that 230 patients had no diagnosis made after admission (31·5 per cent with NSAP). These patients were interviewed by questionnaire 5 years later. The median age of patients with NSAP was 20, with a slight female excess, and 76 per cent had no previous admission for the same problem. At 5 years, 77 per cent had experienced no further attacks of pain and remained well. In the 23 per cent of patients who had experienced further pain reinvestigation allowed precise but very varied pathological diagnoses to be made in 80 per cent of these patients. Eleven patients died, 10 of causes unrelated to the admission for abdominal pain and one of leukaemia infiltrating the abdominal wall. A further study reported that 10·7 per cent of patients over the age of 50 years who presented to hospital with abdominal pain for which no initial cause could be found subsequently developed cancer[8].

The introduction of computer-aided diagnosis for conditions such as acute abdominal pain[9] led to the accumulation of large amounts of data on the symptoms and signs of many common abdominal conditions and must have produced information on the clinical features of NSAP, but so far these details have not been reported. It is noteworthy that the introduction of such a computer-aided diagnostic system led to a 25 per cent drop in 'unnecessary' admissions[9].

It is clear that patients with NSAP constitute a considerable proportion of acute surgical admissions, with important implications for bed occupancy, manpower provision and cost to the health service. Patients with NSAP are usually admitted as emergencies and may reduce the efficiency of operating theatre usage by forcing cancellation of planned admissions. A positive early diagnosis of NSAP would forestall admission to hospital and minimize the waste of resources. The cause of NSAP remains unknown and it is uncertain whether the condition comprises a heterogeneous group of known diseases, or one or more conditions that have, so far, gone unrecognized. The first alternative seems the most likely, and a number of possibilities have been put forward.

Viral infections

Viral infections are common and are often blamed for many undiagnosed transient abdominal pains in patients seen by general practitioners, although virological investigations are rarely performed. Pullan *et al.*[10] studied 181 children in whom appendicitis had been excluded on clinical grounds, performing both culture and antibody screening for viral infection. Ninety-nine (55 per cent) of these children were subsequently diagnosed as NSAP, but a definite diagnosis of viral infection was made in only 18 (18 per cent of children with NSAP). Wenham[11] performed a similar study and found that of 68 children with NSAP 16 (23 per cent) showed evidence of viral infection. Both studies found a wide range of pathogens to be implicated. If these recent studies are representative, viral infection may be the cause of approximately one-fifth of cases of NSAP in children. Viral infection may cause abdominal pain more readily in children, as for example in the production of 'mesenteric adenitis'[12], while the peak incidence of NSAP is in 20-year-old females[7]. There have been no studies to investigate the incidence of viral infection in adult patients with NSAP, so no conclusions can be drawn about the importance of viruses in the aetiology of the condition.

Bacterial infection

Some bacterial infections of the gut may go unrecognized, but acute bacterial gastroenteritis, with its characteristic syndrome of abdominal pain, vomiting and diarrhoea, is unlikely to be

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missed. Pathogens implicated in several studies, principally from Scandinavia, are the Gram-negative bacilli *Yersinia enterocolitica* and *Y. pseudotuberculosis*. Winblad *et al.*[13] studied 95 patients undergoing laparotomy for acute abdominal pain, of whom 45 had acute appendicitis. Of the remaining 50 patients, 26 were found to have serological evidence of yersinia infection. It is noteworthy, however, that 25 patients in this study had evidence of terminal ileitis, a far higher incidence than in British practice. A later report from the same group[14] described 141 patients, in whom appendicitis was excluded at laparotomy, and found 20 patients (14 per cent) to have serological evidence of yersinia infection, most of whom had either terminal ileitis or mesenteric adenitis. More recently Morrison[15] reported serological evidence of yersinia infection in 4 of 24 cases of NSAP in adults, but a larger study by Wenham[11] found no example of yersinia infection in 68 children with NSAP. The last two studies suggest that yersinia infection is an uncommon cause of NSAP in the UK.

Worm infestation

Earlier this century infestation of the gut with parasitic worms was frequently blamed for otherwise inexplicable abdominal pain, and it is interesting to note that less has been heard of this idea over the last four decades. The pinworm (*Enterobius vermicularis*) is the only common parasitic worm causing gut infestation in the UK. The usual site of infestation producing episodes of abdominal pain is the vermiform appendix, although rarely other sites can be involved (see Nutting *et al.*[16] for a review). The presence of worms or their ova in the stools of asymptomatic people is common, especially in children, so that the significance of ova in the faeces of patients with NSAP is uncertain. Most studies to assess the role of pinworm infestation have looked at appendicectomy specimens from patients with non-inflamed appendices, and compared the incidence of infestation to that in patients with appendicitis. A comprehensive early study was performed by Ashburn[17] in the USA. He examined 2317 appendicectomy specimens and found pinworms in 10 per cent of 55 non-inflamed appendices compared with an infestation rate of 3 per cent in inflamed appendices. It is noteworthy that normal appendices constituted only 2·3 per cent of the total, a far lower proportion than found in current British practice. Boulos and Cowie[18] performed a similar study in the UK and found pinworm infestation in 9 per cent of 68 non-inflamed appendices compared with 1 per cent of inflamed appendices. These studies provide circumstantial evidence that at least some abdominal pain leading to laparotomy may be caused by pinworm infestation, but there is no direct evidence of the role of pinworm infestation in patients with NSAP who do not undergo appendicectomy. Worm infestation is seldom mentioned as a cause of abdominal pain in the recent literature, but the implication that it is unimportant may be untrue. It is not surprising that parasitic gut infestations are a much commoner cause of abdominal pain in the Far East; thus Soliman[19], in a study from Egypt, found a 32·6 per cent infestation rate in uninflamed appendices.

Abdominal wall pain

Pain localized to the abdomen may arise from structures in the abdominal wall. Some causes of such pain are obvious, for example abdominal wall haematoma, hernia and shingles. Recurrent pain in other sites, such as the back or shoulders, is common, may be severe, and is variously labelled as 'fibrositis', 'nerve entrapment' or 'muscular strain', although the true pathology is unknown. It has been suggested that a similar process affecting the abdominal wall musculature may be the cause of many cases of NSAP[20]. It has been claimed that the onset of such pain may be related to physical activity, relieved by rest and characterized by a localized tender area in the abdominal wall[20]. Evidence for this hypothesis is sparse.

Mehta and Ranger[21] described 110 patients with a nerve entrapment syndrome, characterized by burning intermittent abdominal pain and the finding of an acutely tender 'trigger area' localized to the outer border of the rectus sheath, best elicited with the abdominal wall muscles tensed. A similar syndrome was reported in 62 patients by Applegate[22]. In Mehta's patients relief was obtained by local anaesthetic infiltration at the 'trigger point', and one-half of the patients obtained permanent relief by the injection of phenol[21]. It is likely that both series are made up of cases collected over a number of years, and provide no clue to the incidence of the condition. The only study to investigate the frequency of abdominal wall tenderness in an unselected population was a prospective study by Thomson and Francis[23] of 120 patients with acute abdominal pain. In this study, the point of maximal abdominal wall tenderness was localized by palpation and it was noted whether the tenderness increased or was unchanged by contracting the abdominal musculature. All 96 patients whose tenderness was unchanged by abdominal muscular contraction were eventually found to have a recognized pathological diagnosis (usually appendicitis). Of 24 patients whose tenderness increased on contraction of the abdominal muscles, 13 had no operation and remained well and 11 had exploratory laparotomies performed of which 10 revealed no pathology and one an inflamed appendix adherent to the anterior abdominal wall.

Irritable bowel syndrome

Irritable bowel syndrome is characterized by recurrent bouts of abdominal pain and increased frequency of bowel habit. The diagnosis is usually made after careful investigation has excluded other causes for the symptoms. The condition is common, especially at a subclinical level and Thompson and Heaton[24], who studied 301 normal adults, found that 14 per cent experienced recurrent symptoms suggestive of irritable bowel syndrome, although only 20 per cent of these had consulted a doctor about the symptoms. It is possible that some patients with NSAP could be suffering from the irritable bowel syndrome, but no studies have been reported which might support this suggestion. A cardinal feature of the irritable bowel syndrome is, however, the chronic and recurrent nature of the pain[25] while 77 per cent of patients attending hospital with NSAP have no further attacks of abdominal pain[7]. It seems unlikely therefore that the irritable bowel syndrome is the underlying cause in many patients with NSAP.

Gynaecological pain

There is an excess of young females among patients admitted to hospital with NSAP[4], and pain arising from the female reproductive organs may be partly responsible. Pelvic inflammatory disease (PID) is a common condition and a variety of sexually transmitted infective agents have been implicated as the cause[26]. Furthermore, the infective processes associated with PID may lead to inflammation affecting other intra-abdominal organs, a classic example of this being perihepatitis following gonococcal[27,28] and non-gonococcal PID[29,30]. The clinical diagnosis of PID is surprisingly difficult to make accurately. For example, Lennart and Westrom[31] found that 45 per cent of 814 women thought, on clinical examination, to have pelvic inflammatory disease were discovered, after investigation, to have either an alternative diagnosis or no diagnosis at all. Since it is so difficult to make an accurate diagnosis of PID, it may well be that this is a 'missed' cause of NSAP, but the incidence of PID in patients with NSAP is unknown.

Mittelschmerz was a term first used by Fehling[32] for pelvic pain occurring in fertile women at mid-menstrual cycle. The prevalence of this symptom in the normal population is uncertain, but O'Herlihey *et al.*[33], who studied 96 women attending an infertility clinic, found that 34 experienced lower abdominal pain at midcycle, and in 25 this was localized to the side of ovulation, determined by ultrasonography.

Mittelschmerz may be the explanation for some NSAP in women but, unlike most cases of NSAP, mittelschmerz tends to be recurrent and cyclical.

Psychosomatic pain

There has always been a tendency to ascribe symptoms and signs caused by unrecognized diseases to psychological or psychiatric causes. There are certainly many surgeons who think that patients with NSAP are often emotionally unstable or have peculiar personalities. It is known that psychological factors have an important role in the genesis of recurrent abdominal pain of childhood[34]. Stickler and Murphy[35] followed 161 children diagnosed as having recurrent abdominal pain due to psychological factors. In 5 years' follow-up only three children subsequently had the diagnosis changed, all to inflammatory bowel disease. The condition can continue into adult life, especially if severe, and Nicol[36], who described 34 intractable cases followed for 28 years, found that 53 per cent continued to have symptoms as adults. There is sometimes an overlap between the two conditions, but NSAP in adults generally has a quite different natural history to that of recurrent abdominal pain of childhood, which, once established, tends to become a conditioned regular pattern of response to psychological pressure.

Overt psychiatric disease may present with symptoms of abdominal pain[37], but the diagnosis is seldom difficult since the patient often has other more obvious features of psychiatric disorder such as hallucinations. There is also evidence that, in the small number of adults who experience chronic NSAP, there is often an underlying psychiatric cause[38–40].

There is little evidence that psychological disorder plays a role in most adults with NSAP. Blanton and Kirk[41] produced a psychological profile of 61 patients after appendicectomy and correlated this with the operative and histological findings. Of 44 patients found to have acute appendicitis, 13 showed evidence of emotional disturbance, while all 17 patients who had normal appendices removed were emotionally disturbed. A similar study some 20 years later of 61 men undergoing appendicectomy[42] showed a more clearcut division: all 48 patients with inflamed appendices were psychologically normal, while all 13 with normal appendices showed evidence of emotional abnormality. A contemporary study of 118 women presenting with right iliac fossa pain found that 26 per cent subsequently had no pathological diagnosis made, and suggested that 'emotional factors' accounted for a high proportion of these cases, although a formal psychological assessment was never made[3].

Creed[43] interviewed patients after appendicectomy to assess the number and severity of 'life events' one year before surgery, the interview being repeated one year after surgery. The 56 patients who had had a histologically normal appendix were found to have had significantly more 'severe life events' before appendicectomy than after appendicectomy, and significantly more than patients who had inflamed appendices, or than a matched normal control group. The validity of psychological assessments performed so soon after a major operation is doubtful, however, as is the relevance of the studies to the majority of patients with NSAP, who never have an operation for their abdominal symptoms. A recent study used more objective assessments of anxiety and depression, comparing an 'organic' group of 87 patients admitted with abdominal pain with a 'non-organic' group of 18 patients, subsequently found to have NSAP. The 'non-organic' patients were almost all female and were found to differ from the 'organic' patient by showing significant psychological abnormality[44]. Again, many of the patients were interviewed immediately after operation.

There is a need for further, larger studies to clarify these issues, although the discordant psychological profiles of surgeon and psychiatrist may prove to be an insurmountable obstacle to such co-operative research projects.

Miscellaneous conditions

The diversity of suggested causes of NSAP are a tribute both to human ingenutiy and the difficulty of diagnosis in this condition. Lactose intolerance was first described as a cause of recurrent abdominal pain in children[45,46] but has since been recognized in adults and may well be the correct diagnosis in some patients previously thought to be suffering from the irritable bowel syndrome[24]. Discitis[47,48], abdominal epilepsy[49] and abdominal migraine related to food allergy[50] are all uncommon causes of abdominal pain, and therefore likely to explain only a few cases of NSAP.

Patients with NSAP account for one-third of all acute hospital surgical admissions with pain in the abdomen. Non-specific abdominal pain therefore constitutes a problem of considerable clinical and economic importance to which too little attention has been devoted. The natural history of the condition has been well documented, but no prospective study has been reported of the detailed symptomatology and physical findings displayed by patients with this disorder. It remains uncertain whether NSAP constitutes a single disease entity or, as seems more likely, is simply the presenting symptom of a large number of minor and self-limiting conditions. At present, the diagnosis of NSAP is made retrospectively and by exclusion. Considerable savings in manpower and resources could be made by better definition of the clinical features of this condition to allow prospective diagnosis and more appropriate management. Patients admitted to hospital with acute NSAP represent only the tip of the iceberg of the problem. Many patients with NSAP are managed entirely by their general practitioners while others are referred to hospital but not admitted. Comparison of symptomatology and physical findings between these three groups of patients might well shed more light on this condition.

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Choledochoduodenostomy for intrabiliary rupture of hydatid cysts of liver

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Frank intrabiliary rupture is an important complication of liver hydatid cysts and its incidence is between 5 and 25 per cent. The main principles of management are the surgical treatment of the cyst with removal of all cystic elements and drainage of the biliary tree. Accurate pre- and intra-operative diagnosis and permanent drainage of the biliary tree by a wide choledochoduodenostomy are important to reduce morbidity and mortality. In this report 28 cases of frank intrabiliary rupture of hydatid cysts treated by choledochoduodenostomy are presented.

Keywords: Hydatid cyst, intrabiliary rupture, choledochoduodenostomy

Intrabiliary rupture, the most common complication of hydatid cysts, has an incidence of 5–25 per cent[1–4]. Dew[5] was the first to report this complication but many reports have since been published[2,3,6–8].

There are two types of communication between the biliary tree and hydatid cysts: frank intrabiliary rupture and simple communication[6]. In the former, the elements of the cyst drain into the biliary ducts and cause intermittent or complete obstruction. Simple communications are frequently seen during hydatid cyst surgery and can cause postoperative biliary fistulae unless they are properly treated by closing the openings. By contrast, frank intrabiliary rupture should be diagnosed pre-operatively, explored carefully during the operation and treated by biliary drainage to prevent severe complications, particularly cholangitis and biliary obstruction by cyst contents.

We present 28 cases of frank intrabiliary rupture and describe our policy of surgical management.

Patients and methods

In the 10 year period 1977–86, 28 patients underwent operation for frank intrabiliary rupture of a hydatid cyst in the Surgical Department of Istanbul Medical School. During the same period a total of 174 patients were operated on because of hydatid disease of the liver. There were 16 males and 12 females with an age range of 11–69 years (mean 41). The duration of symptoms ranged from 2 to 24 months. The first six patients have already been reported[7].

The most common symptoms and physical findings are shown in *Table 1*. The main diagnostic investigations were X-ray of the abdomen and chest, ultrasonography and scintigraphy. During operation intra-operative cholangiography or injection of methylene blue or air into the common bile duct was used to demonstrate the communication between the cyst(s) and the biliary tree. Simple communications without associated cholangitis, jaundice, enlargement of the common bile duct or any cyst elements in the duct were not included in this report. Exploration of the common bile duct and side-to-side choledochoduodenostomy with two layers of interrupted sutures were performed for all cases of frank intrabiliary ruptures. The cysts were treated by external drainage, cystectomy or closure of the cavity by introflecting sutures (obliterating the residual cavity by introflecting the cyst wall and adjoining liver parenchyma with sutures).

Results

The main diagnostic X-ray findings were elevation of the right diaphragm, right pleural effusion, calcification and air–fluid levels in the right upper quadrant. Ultrasonography was performed in 17 cases and demonstrated cysts in 16 (94 per cent), but the common bile duct was dilated in only 4 cases. Liver scan showed a filling defect in 11 of the 12 cases in which it was performed. Percutaneous transhepatic cholangiography revealed the communication in two cases.

The results of laboratory findings are outlined in *Table 2*. The Casoni test was positive in 12 and the Weinberg test in 10 of 22 cases. Raised white blood count, alkaline phosphatase and bilirubin were the other main laboratory findings.

During operation the common bile duct was explored in every case. The diameter of the duct ranged from 2·0 to 4·2 cm (average 2·3 cm). The right lobe of the liver was involved in 18 cases, the left lobe in 10 cases. The diameters of the cysts ranged from 10 to 18 cm. A large communication between the cyst and the biliary tree was demonstrated by intra-operative cholangiography in 12 patients. In five patients methylene blue or air was injected into the common bile duct and appeared in the cyst which identified the communication.

During the exploration of the common bile duct vesicles, debris or purulent material were found in 23 cases. In five patients there was no cyst material but a large communication was detected. After treatment of the cyst cavity by external drainage in 14 cases, introflection in 10 cases and cystectomy in 4 cases, the common bile duct was drained in all patients by a choledochoduodenostomy. T tube drainage was also performed in two patients.

Four patients required reoperation. T tubes became occluded in two patients and choledochoduodenostomy was performed at

Table 1 *Main symptoms and clinical findings in 28 patients with intrabiliary rupture of hydatid cysts*

Symptoms and clinical findings	No. of patients (%)
Fever	25 (89)
Pain	23 (82)
Jaundice	16 (57)
Epigastric discomfort, fatigue, nausea	21 (75)
Epigastric mass or nodular hepatomegaly	11 (39)
Diffuse hepatomegaly	10 (36)
Rebound tenderness	4 (14)

Table 2 *Laboratory investigations in 28 patients with intrabiliary rupture of hydatid cysts*

	No. of patients	Positive results (%)
Elevated white blood count	28	26 (93)
Elevated alkaline phosphatase	26	21 (81)
Elevated serum bilirubin	26	16 (62)
Casoni test	22	12 (55)
Weinberg test	22	10 (45)

the second operations. In one patient, choledochoduodenostomy was only performed as an emergency procedure for suppurative cholangitis and the cyst was drained at a second operation. The fourth patient was transferred from another hospital, with the findings of suppurative cholangitis 15 days after drainage of the cyst. The cystic elements were removed from the common bile duct and choledochoduodenostomy was performed at the second operation. She underwent surgery again for obstruction of the common bile duct by cystic elements and U tube drainage was performed. This patient died of septicaemia on the seventh postoperative day.

The average hospital stay for the 28 cases was 14·2 days. The main postoperative complications were wound infection in five, pulmonary infection in four, and cholangitis in three patients. In the postoperative period the average duration of external bile drainage from the cyst cavity was 2·4 days and the amount of bile drained was 80 ml/day. The follow-up period ranged from 3 months to 10 years (average 4·2 years). In the late postoperative period only two cases had cholangitis due to the passage of cyst elements through the choledochoduodenostomy. In the first patient the symptoms appeared 4 months after the operation and resolved on conservative therapy. In the second patient, investigation showed partial obstruction at the level of the anastomosis 8 years after the operation. The occluding membrane was removed endoscopically and all the symptoms of cholangitis disappeared. No patient underwent late surgery for reasons related to the hydatid disease.

Discussion

Hydatid cysts of the liver cause pressure on the surrounding parenchyma and many cysts leak into a small duct or rupture into a larger one[8]. The pressure inside these cysts is always higher than the pressure in the biliary tract and after rupture the cyst elements pass into the biliary ducts. The liver cyst material does not die in the biliary channels and may cause obstruction and cholangitis at any stage of their life cycle[9].

A definite pre-operative diagnosis can be established in most patients by a careful history, physical examination and investigation. In areas where the disease is endemic, any patient having fever with rigor, jaundice and pain in the right upper quadrant, with or without enlargement of the liver or a palpable abdominal mass, should be regarded as a case of intrabiliary rupture of hydatid cyst until proved otherwise[7,10–12]. The diagnosis is usually best established by ultrasonography[2,12,13]. In an endemic area, a space occupying lesion of the liver and an enlarged common bile duct should be accepted as strong evidence of intrabiliary rupture. In suspected cases, endoscopic retrograde cholangiopancreatography provides a safe and accurate pre-operative assessment and endoscopic sphincterotomy allows the patient to undergo elective surgery in an improved condition once the suppurative cholangitis has settled[12,14,15]. Although there are no published reports of peritoneal spread due to percutaneous transhepatic cholangiography[16], this invasive method in our opinion is contra-indicated during the investigation of hydatid disease.

Intra-operative diagnosis is very important when the pre-operative investigations do not reveal the communication. The presence of a dilated common bile duct with a liver cyst is an indication for duct exploration. Peroperative cholangiography or injection of air or methylene blue should be done in every case.

There are two stages of the operation. The first is the surgical treatment of the cyst. The other is the exploration and drainage of the common bile duct. From the point of view of the intrabiliary rupture any technique can be used for the cyst cavity but the removal of all the cystic elements is important. Drainage of the dilated common bile duct may be essential to avoid death from suppurative cholangitis or septic shock[2,5,14]. Most authors prefer T tube drainage (*Table 3*): our experience has, however, shown that T tube drainage is insufficient and hazardous. A T tube provides only temporary drainage and after tube removal, overlooked debris or daughter cysts in the biliary tree can obstruct the duct. The T tube itself can even cause obstruction in the postoperative period[6,8,15] because its diameter is always smaller than that of the duct. T tube drainage is, in addition, always a source of infection in the biliary tree, causes loss of the bile, lengthens hospital stay and eventually increases morbidity and mortality[17].

Some authors have used cystojejunostomy in the treatment of intrabiliary rupture[1,3]. This technique can be used only when the cyst has a mature wall and it only prevents external bile loss. Even with this form of internal drainage some elements of the cyst can obstruct the biliary tree and cause cholangitis. Some surgeons have preferred sphincteroplasty to choledochoduodenostomy[15]. Sphincteroplasty is suitable for a non-dilated duct but always carries a higher mortality and morbidity rate than choledochoduodenostomy.

The wide biliary intestinal anastomosis provided by choledochoduodenostomy is generally sufficient for the passage of retained debris in the early or late postoperative period. In spite of this wide opening the anastomosis may become obstructed by cystic elements. The pressure inside the biliary lumen can push the debris into the duodenum but if it is insufficient to open the passage, cholangitis and jaundice occur. In these circumstances the obstructing element can easily be removed by an endoscope through the biliary intestinal anastomosis.

Choledochoduodenostomy is usually technically straightforward and we believe that it offers the most effective and uncomplicated way to drain the common bile duct following intrabiliary rupture of hydatid disease.

Table 3 *Summary of previous reports of the intrabiliary rupture of hydatid cysts*

Author	Year	No. of cases	Total no. of cases of hydatid cysts	Main method of biliary drainage
Dagher[20]	1954	3	44	T tube
Hankins[6]	1962	4	39	T tube
Harris[8]	1965	2	—	T tube
Al Hashimi[21]	1971	3	78	T tube
Kattan[10]	1973	15	136	T tube, dilatation of sphincter of Oddi
Barros[1]	1978	36	212	Cystojejunostomy or gastrostomy
Mustafa[18]	1978	1	—	T tube
Sayek[4]	1980	5	100	T tube
Dugalic[17]	1982	2	204	T tube
Lloyd-White[22]	1982	110	—	T tube
Langer[23]	1983	11	40	External drainage of the cyst
Dadoukis[11]	1984	45	265	T tube
Ovnat[2]	1984	4	14	Choledochoduodenostomy (for suppurative cholangitis)
Lygidakis[3]	1984	39	417	T tube
Elhamel[19]	1986	2	50	T tube

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Random control trial of a short course of aspirin and dipyridamole (Persantin) for femorodistal grafts

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The effect of a short course of anti-platelet agents, started pre-operatively, on the patency of femorodistal bypass grafts is unknown. One hundred and forty-eight such grafts were randomized to act as controls or to receive dipyridamole 200 mg b.d. for 48 h pre-operatively and dipyridamole 200 mg b.d. with aspirin 300 mg daily for 6 weeks after surgery. Patients were well-matched and the mean pre-operative pressure index of 0·37 rose to 0·78 during the first postoperative week. No deaths were attributable to the treatment. Ninety-three grafts were autogenous vein and the remainder were prosthetic (GORE-TEX (PTFE), human umbilical vein or externally supported Dacron). At 1 year autogeneous vein cumulative patency was 75 per cent. Overall results showed higher patency in the treated group* (P = *0·012) which was entirely accounted for by the difference between prosthetic dipyridamole and aspirin group (85 per cent patency) and prosthetic control groups (53 per cent patency,* P = *0·005) and arose during the first postoperative month. There were 11 deaths and 8 amputations in the dipyridamole and aspirin group and 8 deaths and 12 amputations in the control group. It is concluded that a six week perioperative course of dipyridamole and aspirin allows the patency of prosthetic femorodistal bypass to approach that of autogenous vein, and the regimen therefore is recommended for patients who may require a prosthetic graft.*

Keywords: Vascular surgery, femorodistal bypass, antiplatelet agents, graft occlusion

Autogenous vein remains the conduit of choice for femorodistal grafting despite reports of occlusion rates as high as 30 per cent during the first 12 months[1–3]. The failure rate of prosthetic grafts may be higher, especially when inserted below the knee, so these grafts should be reserved for cases of critical ischaemia where autogenous vein is not available. Technical problems may cause the failure of both graft types but there are other reasons for failure, one of which is high thrombogenicity immediately after surgery, particularly in prosthetic grafts[4,5]. Platelet inhibitors have been shown to improve early patency in coronary artery grafts[6,7] and some prosthetic grafts in the femorodistal position[8–10] when given in prolonged courses. Therefore, we conducted a randomized controlled trial of a 6-week course of aspirin and dipyridamole started pre-operatively in patients undergoing either autogenous vein or prosthetic graft femorodistal bypass, to discover whether improved patency could be achieved by a short course of anti-platelet therapy covering the observed period of maximum thrombogenicity.

Patients and methods

The patients were studied during treatment at the vascular unit of the Royal South Hants Hospital, Southampton. There were 140 patients who underwent 148 femorodistal bypasses for rest pain (98) or very short distance claudication (42). Twenty-eight patients were undergoing secondary reconstructions. Each patient's clinical history included claudicating distance, duration of symptoms, sex, age, diabetes and smoking habits, while examination included Doppler measurement of ankle blood pressure and arteriography. Before surgery patients were allocated randomly to receive active treatment or to act as controls. The active treatment regimen (dipyridamole and aspirin) was as follows: 48 h pre-operatively – dipyridamole 200 mg b.d. orally; day of surgery with premedication – dipyridamole 200 mg orally; postoperatively – dipyridamole 10 mg IV t.d.s.; for 6 weeks thereafter — dipyridamole 200 mg b.d. orally and aspirin 300 mg daily orally.

Control patients received no specific anti-thrombotic treatment. Aspirin was not given pre-operatively because of the theoretical risk of bleeding from peptic ulceration at a time of stress in patients with vascular disease[11]. Dipyridamole was given postoperatively on the day of surgery by slow intravenous infusion once the patient was haemodynamically stable. Platelet function was not tested.

All the operations were carried out by four surgeons using similar techniques. Where possible autogenous vein grafts were used, initially in the reversed fashion but later by the *in situ* technique. When saphenous vein was not available each surgeon chose his preferred prosthetic graft: human umbilical vein, thick walled GORE-TEX or externally supported Dacron. All surgeons used heparin and sutured with continuous Prolene. Redivac drains were inserted and postoperative blood loss recorded. In addition to clinical determination of patency, patients underwent Doppler ankle blood pressure readings before discharge from hospital and at follow up 1, 3, 6 and 12 months after surgery. Where a further operative procedure was being considered, arteriography was performed.

The endpoints of the study were graft failure, limb loss, death and 12 months follow-up. The results were analysed by life table analysis[12] using BMDP Statistical Software.

There were 70 grafts in patients allocated to the control group and 78 in the treated group. The groups compared well (*Table 1*) with both pooled and separate *t* tests showing no significant differences. The number with rest pain (98, 66 per cent) and the low mean pressure index at presentation (0·37) indicate the severity of ischaemia in the study patients. There was no difference in the perioperative blood loss and no significant difference in the numbers of patients requiring immediate re-operation for bleeding. The mean pressure index rose from 0·37 pre-operatively to 0·78 by the end of the first week after surgery.

Results

One hundred and seven grafts were undertaken in male patients and forty-one in females. The distribution of the grafts is shown in *Table 2*. Ninety-three (63 per cent) of these were autogenous

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vein grafts and the three types of prosthetic graft were evenly spread among the remainder. One hundred and nineteen of these grafts were inserted below the knee: eighty-two of these (69 per cent) were autogenous vein.

Six patients in the treatment group (8 per cent) complained of headaches or severe malaise. Two of these could not comply with the regimen and therefore were withdrawn from the study. One patient developed severe angina soon after admission to hospital and died a month later of myocardial infarction. One further patient who received treatment died of myocardial infarction 24 h after surgery but was included in the analysis. The treatment was not associated with gastrointestinal haemorrhage, although there was one death from peptic perforation in the control group.

Overall graft survival at 12 months in the treated group was 84 per cent, in contrast with 65 per cent in the controls ($P = 0·012$, generalized Wilcoxon, Breslow). In below-knee grafts alone this difference did not attain statistical significance (83 per cent in the treated group, 68 per cent in the controls, $P = 0·069$). Treatment made no difference to the 12-month survival of autogenous vein grafts (83 per cent in the treated group, 72 per cent in the controls, $P = 0·317$ for all autogenous vein grafts; 83 per cent in the treated group, 73 per cent in the controls, $P = 0·398$ for below-knee autogenous vein grafts) but, in contrast, there was a striking difference in 12-month survival between the prosthetic graft groups (85 per cent in the treated group, 53 per cent in the controls, $P = 0·005$ for all prosthetic grafts; 83 per cent in the treated group, 58 per cent in the controls, $P = 0·037$ for below-knee prosthetic grafts).

Table 1 *Differences in variables between treated and control groups*

	Control ($n = 70$)	Treated ($n = 78$)	P
Non-smokers	27	30	0·99
Diabetic patients	9	10	0·99
Duration of intermittent claudication (months, ±s.d.)	24·7±35·0	15·6±24·9	0·07
Claudicating distance (yards, ±s.d.)	108±82	120±150	0·54
With rest pain	42	46	0·90
Rest pain duration (weeks, ±s.d.)	4·6±8·4	5·8±18·0	0·61
Distal run-off; number of vessels			
1	17	17	0·72
2	14	9	0·16
3	36	51	0·09
Grafts from superficial femoral artery	4	3	0·45
Below-knee graft insertions	55	64	0·60
Single calf vessel insertions	6	8	0·73
Pre-operative pressure index* (±s.d.)	0·35±0·27	0·39±0·25	0·38
Operative blood loss (ml, ±s.d.)	498±396	520±470	0·76
Immediate reoperations for haemorrhage	1	7	0·27

P, calculated separately; for pooled t value, $P = 0·63$

$$* \text{ Pressure index} = \frac{\text{ankle systolic blood pressure}}{\text{brachial systolic blood pressure}}$$

Further analysis of the prosthetic graft groups showed that treatment increased PTFE graft 12 month patency (dipyridamole and aspirin group patency 11 out of 13, control 4 out of 9, $P = 0·030$, *Table 2*) and human umbilical vein graft patency (treated group patency 8 out of 9, control 3 out of 8, $P = 0·011$), whereas it made little difference to the Dacron graft patency (treated group patency 5 out of 7, control 7 out of 9, $P = 0·710$).

All the differences arose during the first postoperative month (*Figure 1*).

There were further operations on 26 limbs, mostly during the first 4 months postoperatively. These comprised 16 primary amputations and 10 second reconstructions of which 4 eventually resulted in amputations; thus 20 limbs were lost overall (14 per cent). Seven of the amputations were below the knee, eight through and five above the knee; type of graft and treatment did not affect the site of amputation. Treatment made

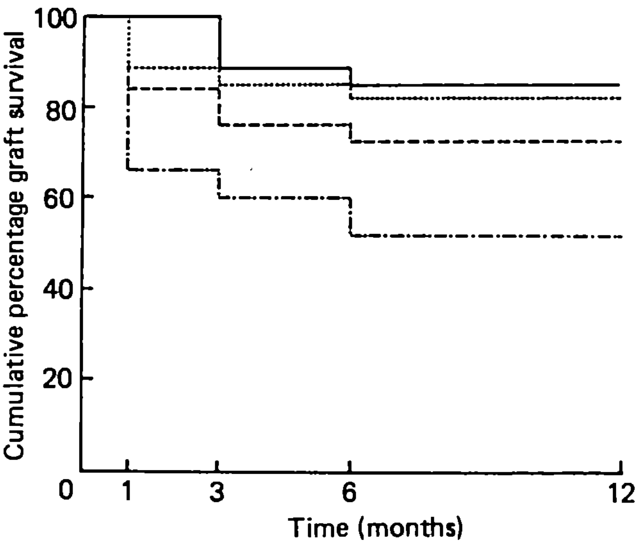

Figure 1 *Patency rate curve for all grafts divided according to the nature of the graft: —— prosthetic graft in trial; ······ autogenous vein graft in trial; ---- autogenous vein graft, control; –·–·– prosthetic graft, control*

Table 2 *Distribution of graft types and failures of prosthetic grafts*

Trial status	Graft type								Numbers at risk (all grafts)	
	Autogenous vein		Prosthetic							
	Reversed	*In situ*	PTFE		Human umbilical		Dacron			
	n	n	n	fail	n	fail	n	fail	0–1 months	6–12 months
Control	18	26	9	5	8	5	9	2	69·5	21·5
Treated	17	32	13	2	9	1	7	2	76·0	29·5
Total	35	58	22	7	17	6	16	4		
P	0·705		0·030		0·011		0·710			

P probability, generalized Wilcoxon (Breslow), control *versus* dipyridamole and aspirin treated group, fail = fail by 12 months no difference to the number of amputations (treated $n=8$, control $n=12$) except in the prosthetic graft group, where there were more amputations among the control patients (7 out of 26) than the treated patients (3 out of 29). This did not reach statistical significance ($P=0\cdot097$) but was much greater than any other difference and occurred during the first 2 months postoperatively.

There were 19 deaths during the study, one of which was in a patient who had entered the trial for bilateral surgery. There was no difference in mortality between treated ($n=11$) and control ($n=8$) groups ($P=0\cdot462$). This was also true when cardiovascular deaths were considered alone (treated 5, control 2, $P=0\cdot311$).

Symptoms were recorded during follow-up. When divided into groups with no symptoms, intermittent claudication or rest pain there was no difference except at 1 month in the prosthetic graft group, where none of the treated patients was symptomatic ($\chi^2=8\cdot10$, $P=0\cdot017$, 2 d.f.). After 3 months 2 of the 22 in this group had developed intermittent claudication and 2 rest pain.

Discussion

All grafts appear to be most thrombogenic in the early hours and days after insertion[13]. This relates to the characteristics of the graft itself and also the healing process across the anastomosis[14–16]. By 6 weeks the most thrombogenic phase appears to be over, although platelet deposition on prosthetic grafts may continue for many months[17,18]. The decision to limit treatment to the first 6 weeks postoperatively and to start the regimen before surgery was taken on this basis, although the benefits of this are as yet unproven[19]. The results vindicate these assumptions.

Dipyridamole and aspirin treatment may decrease platelet deposition and thrombus formation on a newly implanted graft and it may also reduce the neo-intimal hyperplasia which occurs during the first few months after surgery[20]. Despite the fact that platelet function is affected by autogenous vein grafts[21] and that dipyridamole and aspirin treatment appears to decrease neo-intimal hyperplasia in both experimental[22] and coronary vein grafts[7], we were unable to show any beneficial effect on femoro-distal autogenous vein grafts. This finding contradicts Cheseboro *et al.*'s work[6]; however, the coronary vasodilator effect of dipyridamole may explain the difference.

The overall patency rate in the treated prosthetic graft group was similar to that of both groups of autogenous vein grafts. These results are similar to those reported by Donaldson *et al.*[22] and Oblath *et al.*[14] although they used continuous treatment in contrast with our limited 6-week regimen. Moreover, the results were unaffected by the relationship of the distal anastomotic site to the knee.

Although the numbers in the subgroups of prosthetic grafts were small, the increased patency achieved in the treated PTFE and human umbilical vein groups in comparison with their controls fitted with Goldman *et al.*'s assessment of thrombogenicity[23]. The more satisfactory performance of Dacron grafts was also confirmed in an extended study[24].

We were unable to show any increase in operative blood loss in the treated group which may reflect the decision not to give aspirin pre-operatively, although small doses of aspirin in combination with dipyridamole do not affect bleeding time[25]. Despite this, seven early reoperations were required for bleeding in the treated group in contrast with only one in the controls ($t=1\cdot11$, $P=0\cdot27$).

We feel justified in recommending a 6-week course of dipyridamole and aspirin, started pre-operatively, in patients undergoing femorodistal bypass when a prosthetic graft may be required. The benefits of perioperative treatment are reflected by prosthetic graft patency increased to the equivalent of autogenous vein at 1 year.

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Distal arterial bypass by composite grafting

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The use of non-autogenous prostheses for femorodistal grafting has been attended by relatively poor patency rates. We have attempted to improve on these disappointing results by fashioning a composite graft using expanded PTFE (GORE-TEX) and transposed non-reversed saphenous vein, placed between the femoral artery and anterior tibial artery. We report the early results using this technique in 25 critically ischaemic limbs. At 12 months, the cumulative graft patency for this group of patients was 65 per cent (mean follow-up of 19 months). Eighteen of the twenty-five limbs were saved and there was no mortality. This technique offers a useful alternative to other forms of distal grafting and appears superior to the results obtained using non-autogenous femorodistal conduits.

Keywords: Femorodistal bypass grafting, composite graft

Femorodistal bypass grafting offers a method of saving the critically ischaemic lower limb. The technique is now widely accepted and practised, but the success of the procedure varies with the material used for the bypass conduit.

Present evidence suggests that the most suitable bypass graft is the saphenous vein, used *in situ* in preference to the reversed graft. However, in many cases, the vein is neither available in sufficient length, nor of suitable calibre, certainly for the reversed technique where a vein diameter of 4 mm is recommended. Studies of alternative graft materials, human umbilical vein or expanded PTFE, have produced inconsistent, but generally unsatisfactory, results and their use in distal reconstruction is probably not justified[1]. The technique of composite grafting with PTFE and autogenous reversed vein has been described, but problems exist because of lumen disparity at the anastomoses.

We describe a conduit, a composite graft of GORE-TEX* and transposed non-reversed saphenous vein running from the femoral artery to the anterior tibial artery, and report the early results.

Patients and methods

Over a period of 21 months, 25 bypass grafts were performed on 24 patients using the composite graft technique described below. One patient underwent surgery to both limbs, with an interval of 3 weeks. Arteriography was performed pre-operatively on all patients, either by the translumbar route or via the femoral artery using the Seldinger technique. The operation was performed under general anaesthesia, with single dose peroperative antibiotic prophylaxis. In six early grafts, conventional 6 mm GORE-TEX was used; in the remainder, we used 6 mm thin-walled GORE-TEX. The composite anastomosis was fashioned above the knee to avoid the need for GORE-TEX to cross the knee joint.

Aspirin, 300 mg once daily, and dipyridamole, 100 mg three times daily, were prescribed postoperatively, but no other anti-coagulation methods were used. Early mobilization was encouraged. The patients were followed up at 3 month intervals after discharge from hospital and patency of the graft assessed clinically and by Doppler pressure measurements.

The series included 14 men and 10 women with an age range of 52–78 years (mean age 66·6 years). Nine patients (38 per cent) were diabetic, 6 controlled on oral hypoglycaemic agents, and 3 on insulin. Fifteen patients (63 per cent) were smokers up to the time of surgery, and a further four patients had been smokers in the past. In two limbs, ipsilateral femoropopliteal *in situ* vein grafts had previously been performed and had occluded. In both cases, further vein was harvested from the contralateral limb.

Almost all operations were performed for limb salvage. The indications for surgery are shown in *Table 1*. Pre-operative ankle/brachial Doppler pressure indices were recordable in 10 patients: the mean pressure index was 0·25 (range 0·20–0·32).

All patients were shown to have a patent anterior tibial artery on pre-operative arteriography. There was single vessel run-off in 13 limbs (52 per cent), two vessel run-off in 10 limbs (40 per cent), and three patent vessels in 2 limbs (8 per cent).

Technique

The anterior tibial artery is exposed through a lateral incision and a 4 cm length mobilized. Topical papaverine is applied. The femoral vessels are exposed through a longitudinal incision and control of the superficial femoral, common femoral and profunda femoris arteries achieved with slings. The long saphenous vein is mobilized distally from the saphenofemoral junction to provide an adequate length of vein to run from the lower thigh to the anterior tibial artery.

After an intravenous bolus injection of 5000 units of heparin, clamps are placed across the groin vessels and a longitudinal arteriotomy of approximately 3 cm is made in the common femoral artery. Heparinized saline is instilled into the vessels. The proximal anastomosis of 6 mm GORE-TEX to the common femoral artery is constructed by an end-to-side technique using continuous 5/0 Prolene. A clamp is placed across the graft and a satisfactory anastomosis confirmed. A 4 cm longitudinal incision is made on the lateral aspect of the lower thigh and the GORE-TEX graft tunnelled using a long aortic clamp.

An adequate length of long saphenous vein is removed and branches ligated with silk or clips. The composite anastomosis unites the GORE-TEX graft and the proximal end of the long saphenous vein in an oblique fashion using continuous 6/0 Prolene. With the clamp removed from the proximal graft, the competent valves prevent blood flow. A Cartier valve stripper is passed up the vein to destroy the valves and achieve flow. The vein is then tunnelled from the distal incision.

With the anterior tibial artery controlled, the oblique distal end of the long saphenous vein is anastomosed to a 1·5–2 cm longitudinal arteriotomy using continuous 6/0 Prolene. Wounds are closed with suction drainage, subcutaneous catgut and skin clips.

Table 1 *Indications for bypass surgery*

Rest pain	14 (46%)
Necrosis/ulceration	2 (8%)
Rest pain and necrosis	8 (32%)
Severe claudication	1 (4%)

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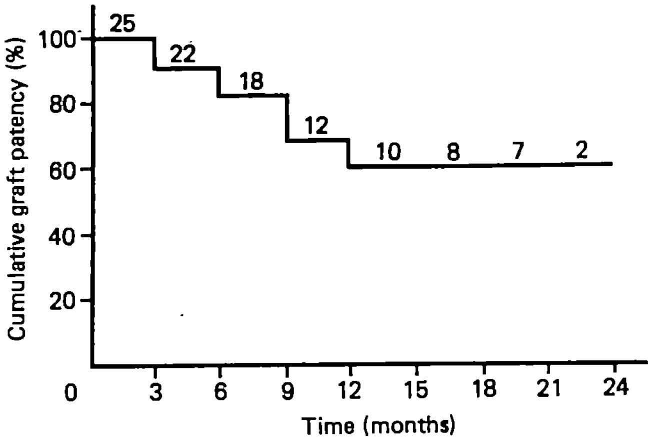

Figure 1 *Cumulative graft patency rate for distal bypass with the composite graft (numbers at risk shown)*

Results

The patency rate of the graft and limb survival have been calculated by the life table method[2]. The cumulative graft patency rate is depicted in *Figure 1*. The overall probability of patency at 12 months is 65 per cent with a mean follow-up of 19 months. Ankle/brachial Doppler pressure indices were measured in the postoperative period; the mean pressure index for the patent grafts was 0·89 (range 0·62–1·3). In the grafts that failed, the pressure indices returned to the pre-operative values.

Nine (36 per cent) of the twenty-five grafts are known to have occluded. Three grafts at the beginning of the series occluded in the early postoperative period; thrombectomy and revision of the distal anastomosis was successful in two cases. Eight grafts occluded between 2 and 11 months after surgery (mean 6·1 months); thrombectomy and revision were attempted in four cases but without success. Of the nine limbs with occluded grafts, five proceeded to below-knee amputation and one to above-knee amputation. Three cases retained a viable limb not requiring amputation despite graft occlusion. One below-knee amputation was performed for rest pain despite a patent graft.

Minor wound sepsis was experienced in three cases and haemorrhage from the proximal anastomosis in one case. One patient had a myocardial infarction in the early postoperative period. There was no perioperative mortality.

Discussion

Femorodistal grafting is a worthwhile procedure if it can be shown to save the critically ischaemic limb and prevent amputation. The major problem is the ideal choice of graft material and, to an extent, the site of the distal anastomosis. We have described a technique which may offer a satisfactory conduit for bypass grafting.

If the popliteal artery is occluded, a decision must be made to bypass on to one of the three distal arteries. The anterior tibial artery is suitable because of its relatively superficial position and accessibility on the anterolateral side of the leg.

A cumulative graft patency rate of more than 80 per cent at 12 months has been reported using the *in situ* vein graft for infrapopliteal bypass[3]. This technique requires the presence of a vein of adequate distal calibre. Situated on the medial aspect of the knee, the distal saphenous vein has to be extensively mobilized to join on to the anterior tibial artery and runs a circuitous route. The patient must be fit to withstand the necessary prolonged anaesthesia. However, the technique offers a relatively non-thrombogenic graft with appropriate flow characteristics, anastomosing vessels of comparable lumen diameter.

Results with bypass grafting vary widely, presumably due to variation in patient selection and operative technique. However, consistently poor results are obtained using non-autogenous conduit materials in femorodistal grafting. A recent study using glutaraldehyde-stabilized human umbilical vein for femorotibial grafting produced a cumulative patency of 28 per cent at 1 year, falling to 9 per cent at 2 years[4], although in contrast, Dardik achieved a patency rate of 67 per cent at 1 year[5]. Using GORE-TEX in the femoropopliteal position, graft patency rates have varied from 63 per cent at 1 year[6] to 29 per cent at 2 years[7]. Although readily available and simple to insert, distal anastomoses with non-autogenous grafts are generally not favoured.

The use of composite grafts was first described in 1962[8]. Recently, composite grafts of GORE-TEX and reversed autogenous long saphenous vein have been used for distal revascularization of ischaemic lower limbs. The results achieved include: 63 per cent patency after mean follow-up of 11 months (24 cases)[9]; 65 per cent after 24 months (42 cases)[10]; greater than 70 per cent at 12 months (76 cases)[11]. The indication for surgery was limb salvage in approximately 80 per cent of cases and for claudication in approximately 20 per cent of cases. In another series, a patency rate of 81 per cent at 2 years was achieved using this composite graft for limb salvage[12]. The standard technique of composite grafting is simple and relatively quick to perform, as only a short segment of vein has to be harvested. Difficulty is encountered because of lumen disparity between the synthetic material and reversed vein at the site of anastomosis and because the calibre of the reversed vein is often greater than that of the tibial vessels. This produces a suboptimal distal anastomotic configuration.

The described graft of GORE-TEX and transposed non-reversed long saphenous vein evolved as a method of avoiding the problems associated with the various types of conduit. We report a series of 25 cases of femoral artery to anterior tibial artery bypass using a consistent technique by the same operator (S.H.L.). A cumulative patency rate of 65 per cent at 12 months has been achieved (mean follow-up of 19 months) with 60 per cent of grafts being patent in the small number reaching 2 years. Almost all operations were for limb salvage and the need for surgical intervention in the cases reported is indicated by the fact that six of the nine limbs with occluded grafts required amputation.

In the UK, current opinion favours the use of the *in situ* vein for femorodistal grafting and reasonably questions the use of synthetic conduits. We feel that this technique offers a viable alternative method for femorodistal grafting, and is associated with an acceptable patency rate.

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Access for acute haemodialysis: a unique, pulse preserving shunt

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In patients who require immediate haemodialysis for renal failure a Quinton–Scribner shunt inserted at the ankle or wrist provides satisfactory vascular access[1]. Such shunts result in permanent reduction of arterial flow distal to the site of insertion. As a result of this, or because of the presence of occlusive disease, patients with a recurrent need for haemodialysis may eventually exhaust the standard sites for temporary vascular access. Dialysis through a subclavian venous cannula is commonly used but may be difficult to establish and can result in poor quality dialysis. Cannulation of the major limb vessel is contra-indicated by the risk of distal ischaemic complications. However, access to the blood flow in the major vessel may be gained by creating an arteriovenous fistula between the artery and one of its venae commitantes or an adjacent vein. Insertion of the Silastic–Teflon cannula into the venous side of the fistula then allows vascular access without jeopardizing distal arterial flow.

Method

The brachial or superficial femoral arteries are suitable for this method, the technique being the same whichever site is chosen. Under local, regional, or general anaesthesia the artery is isolated together with a suitable adjacent vein (the basilic vein, the long saphenous vein, or a vena commitans). A 1 cm side-to-side arteriovenous anastomosis is made with continuous 6/0 Prolene. The vein distal to the anastomosis is cannulated with a Teflon cannula the tip of which should lie just beyond the distal end of the fistula (*Figure 1*). The proximal draining vein is ligated adjacent to the fistula and a Teflon cannula tied into the vein above this to allow venous return from the shunt tubing which emerges through adjacent stab incisions.

Removal of the shunt is achieved by simple avulsion after a period of occlusion.

Results

The shunt has been constructed in 11 patients over a 7 year period (1979–1985). During this time 354 Silastic–Teflon shunts were inserted for acute vascular access.

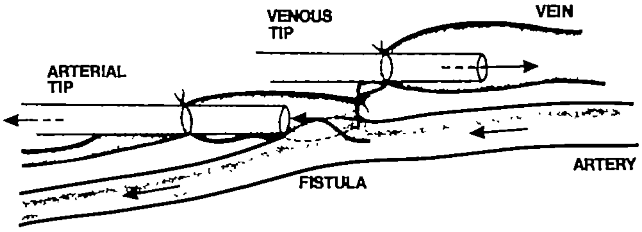

Figure 1 *Illustration of the construction of the shunt. The technique is the same whether the arm or leg is used*

All 11 patients had previously undergone multiple shunt and fistula procedures. The brachial artery was used in eight cases, the superficial femoral artery in three. Median shunt life was 9 weeks (range: 2–38). All shunts provided excellent flow rates for haemodialysis.

Eight shunts were used uneventfully until no longer required. Three shunts failed prematurely. One thrombosed 24 days after construction in a mildly demented patient on warfarin who had been known to tamper with his many shunts in the past. The second failed after developing a leak around the arterial tubing exit site 6 weeks after construction. The third shunt failure occurred in a patient with aggressive systemic lupus erythematosis, after functioning well for 2 weeks. A further patient developed mild ipsilateral arm and forearm oedema whilst under treatment in the intensive care unit. Her shunt function was unaffected. No patients developed distal arterial insufficiency.

There were no cases of haemorrhage or associated complications after removal. Distal pulses, present pre-operatively, were preserved in all patients.

Discussion

This shunt has proved an effective and durable means of vascular access applicable to a small group of problem patients in whom a standard shunt or subclavian cannula are impossible to establish or provide inadequate function.

It provides a satisfactory high flow rate for dialysis. There have been no significant complications associated with its use, and it has been simple to remove using a standard avulsion technique. Despite using the brachial or superficial femoral arteries the technique ensures preservation of distal arterial flow, a major advantage. It has proved greatly superior to an earlier technique which involved the use of a short, free vein graft in which to insert the arterial cannula. This was prone to vein graft angulation and obstruction.

The shunt with its unique preservation of distal limb arterial flow is recommended for use in the few patients in whom standard means of vascular access have been exhausted.

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Prospectively randomized clinical trial to compare in situ and reversed saphenous vein grafts for femoropopliteal bypass

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Two hundred and fifteen femoropopliteal bypass procedures using autologous saphenous vein grafts were randomly allocated to either the reversed or in situ *technique. Eleven veins (5 per cent) were rejected at operation on the basis of their small size, nine in the reversed group and two in the* in situ *group, and there were two (2 per cent) perioperative deaths in each group, leaving 102 reversed and 98* in situ *grafts for further study. The cumulative patency at 3 years of the reversed grafts was 77 per cent and that of the* in situ *grafts was 68 per cent (n.s.). The patency of all grafts was affected adversely by small veins* ($P<0{\cdot}005$)*, long grafts* ($P<0{\cdot}05$)*, low volume of blood flow in the grafts* ($P<0{\cdot}001$) *and poor run-off* ($P<0{\cdot}05$)*. These factors influenced the outcome of the* in situ *and reversed operations to a similar degree and there was no statistically significant difference between them within any subgroup. The mean compliance of the* in situ *grafts measured 3 months or more after operation with an ultrasonic echo-tracking system was $0{\cdot}024 \pm 0{\cdot}01$ per cent/mmHg (± s.d.) compared with $0{\cdot}017 \pm 0{\cdot}01$ per cent/mmHg for the reversed grafts* ($t=2{\cdot}43$, $P<0{\cdot}02$)*. The incidence of fibrous stricture formation as shown by intravenous digital subtraction angiography was 29 per cent in both the reversed and the* in situ *grafts. The results of the study to date indicate that reversed and* in situ *vein grafts are equally effective for femoropopliteal bypass.*

The autologous saphenous vein is firmly established as the best graft material with which to bypass atherosclerotic occlusions in the superficial femoral and popliteal arteries; however, in recent years there has been some controversy concerning the optimum technique for the implantation of these grafts. The vein may be removed completely and then reinserted in an inverted position so as to reverse the direction of blood flow across the valves, the reversed operation, or it may be left *in situ* and the valves rendered incompetent by the passage of a valvulotome, the *in situ* operation.

The reversed operation was the first to be described[1] and following reports of good results in large series[2,3] it rapidly became adopted as the procedure of choice in most centres throughout the world. The *in situ* method[4] has been slower to gain popularity but following the introduction of an efficacious valvulotome[5] and with the added impetus of further refinements of technique more recently[6–9] it has now become the preferred operation in many vascular surgery units.

The *in situ* operation has a number of theoretical advantages over the reversed operation. Firstly, the nutrition of the vein wall by its vasa vasorum is left intact, at least in the central portion of the graft, and this may allow preservation of a number of desirable properties which depend upon tissue viability. For example, a healthy endothelialized flow surface and the continued secretion of plasminogen activators by the wall may promote lower thrombogenicity. Moreover, natural vessel wall compliance may be retained with more efficient transmission of pulsatile energy and less risk of subintimal hyperplasia developing in relation to the anastomoses. Secondly the taper of the *in situ* vein affords better matching for size between the graft and the arteries at both the proximal and distal anastomoses, and furthermore it is said to promote stability of blood flow within the graft. Proponents of the *in situ* technique also claim that it can be used successfully when the vein is too small to be reversed and that it is more suitable for longer grafts to vessels below the knee.

Meticulous surgical technique is essential in order to achieve the best results from both methods but there are a number of specific technical problems associated with the *in situ* operation, the success of which can be jeopardized by anatomical irregularities in the vein, persistent arteriovenous fistulae formed from un-ligated tributaries and by damage to the vein wall caused by the valvulotome[9]. The fate of the disrupted valve cusps is also subject to speculation and it has been suggested that fibrous strictures may develop in relation to them with a threat to the long term patency of the graft[10].

Although there have been an increasing number of claims that the clinical results of the *in situ* technique are superior to those of the reversed operation these are largely based on consideration of the well known theoretical advantages supported by analysis of sequential series of operations. We report here the results of a prospectively randomized study of the two operations to compare their clinical outcome in terms of patency rates over the first 3 years after operation together with an objective assessment of their compliance and the incidence of fibrous stricture formation.

Patients and methods

Patients

Two hundred and fifteen femoropopliteal bypass procedures using autologous saphenous vein grafts were randomly allocated to either the reversed or *in situ* technique. Eleven (5 per cent) of the veins were considered to be excessively small and were rejected at operation, nine in

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Table 1 *Clinical characteristics of patients receiving* in situ *and reversed saphenous vein grafts*

	In situ ($n=98$)	Reversed ($n=102$)	
Age (range)	62 (32–82)	64 (40–80)	n.s.
Male:female	3·6:1	3·6:1	n.s.
Diabetic	15 (15%)	13 (12%)	n.s.
Rest pain/gangrene	66 (65%)	79 (70%)	n.s.
Pressure index (±s.d.)	0·43±0·17	0·40±0·2	n.s.

the reversed group and two in the *in situ* group and there were two (2 per cent) perioperative deaths in each group leaving 102 reversed and 98 *in situ* grafts for further study.

The patients in the two groups were similar in respect of age and sex distribution, their incidence of diabetes and their smoking habits (*Table 1*). Rest pain or gangrene was the indication for surgery in 79 (70 per cent) of the reversed vein operations and in 66 (65 per cent) of the *in situ* operations. In the remaining cases the indication for surgery was disabling claudication. The mean of the pre-operative ankle:arm pressure indices for the reversed vein patients was 0·4±0·2 (±s.d.) and that for the *in situ* graft patients was 0·4±0·17 (±s.d.). An additional procedure to improve inflow in the form of either an aortofemoral or extra-anatomical bypass was performed in a total of 33 patients (16·5 per cent) with 16 in the reversed group and 17 in the *in situ* group.

Operative technique

The reversed vein operation. A suitable length of the ipsilateral long saphenous vein was exposed and excised using interrupted incisions. All tributaries were ligated with fine silk sutures and the graft was gently dilated with heparinized saline solution. The distal anastomosis was constructed first in end-to-side manner using continuous 6/0 Prolene sutures. The site of distal anastomosis was determined by the extent of disease within the popliteal artery and was above the level of the knee joint in 61 cases (60 per cent) and below the knee in 41 cases 40 per cent). The graft was placed superficial to the adductor magnus tendon but otherwise was routed alongside the natural artery in the popliteal fossa and subsartorial canal. The proximal anastomosis was constructed end-to-side to the common femoral artery with continuous 6/0 Prolene sutures. Systemic heparin was not given during or after surgery but heparinized saline was infused locally before the application of clamps.

The in situ *vein operation.* After a small Satinsky side clamp was applied to the common femoral vein, the saphenofemoral junction was divided and the common femoral vein was repaired with a continuous suture of 5/0 Prolene. The first valve was excised under direct vision. Whenever possible the proximal anastomosis was constructed to the common femoral artery in end-to-side fashion using continuous 6/0 Prolene sutures. In 28 instances (27 per cent) the anastomosis could not be constructed at this site without excessive tension and in these cases an anastomosis was made between a short segment of endarterectomized superficial femoral artery and the graft in end-to-end fashion using interrupted 6/0 Prolene sutures. The saphenous vein was then exposed and divided at an appropriate level distally and the valves along the length of the graft were rendered incompetent by the passage of a Hall's valvulotome. Either the 2·5 mm or 3·0 mm diameter valve cutter was used depending on the size of the vein graft. Arterial pressure transmitted through the proximal anastomosis was allowed to distend the vein and fill the valve cusps in order to facilitate the action of the valvulotome. When pulsatile bleeding was observed from the distal end of the graft the distal anastomosis was constructed to the popliteal artery using continuous sutures of 6/0 Prolene. The distal anastomosis was constructed above the level of the knee joint in 56 cases (57 per cent) and below this level in 42 cases (43 per cent). On table angiography was employed in all cases to identify and locate patent tributaries with needles inserted in the skin at intervals along the length of the graft as markers. All tributaries visualized in this way were exposed and ligated in continuity through small skin incisions with minimal dissection of the vein graft. As with the reversed vein operations, dilute local heparin only was used.

Intra-operative measurements. The length and minimum diameter of all of the grafts were determined by direct measurement.

Electromagnetic flowmetry was employed in both types of procedure using a Gould Statham flowmeter type S.P. 2404. On completion of all reconstructions mean volume blood flow was recorded before and after papaverine 30 mg was injected directly into the grafts.

Follow-up procedures. All patients were examined at regular intervals after operation and graft patency was determined by clinical examination together with non-invasive assessment with a Doppler ultrasonic flow probe.

Digital subtraction angiography. All clinically patent grafts were imaged by intravenous injection digital subtraction angiography on one occasion at least 3 months after operation and the angiograms were examined for the presence of fibrous strictures.

Measurement of graft compliance. An ultrasonic phase-locked echo-tracking system[11,12] was used to measure the diastolic graft diameter and changes in diameter with the pressure pulse transcutaneously in 19 reversed grafts and 26 *in situ* grafts. The pressure pulse was recorded indirectly using a sphygmomanometer and stethoscope and compliance was calculated from the percentage change in diameter over the diastolic diameter of the graft divided by change in pressure. All measurements were made at least 3 months after operation in order to eliminate the variability in compliance which occurs initially following implantation[13].

Results

Graft patency (Figure 1)

In the reversed vein group there were 13 failures within the first 3 months after operation and another 5 grafts became occluded during the following 3 years, giving a cumulative patency rate at 36 months of 77 per cent. In the *in situ* group there were 14 early failures and another 11 grafts became occluded during the next 3 years giving a cumulative patency rate at 36 months of 68 per cent. The difference in cumulative rates between the two groups was not statistically significant (Lee–Desu statistic = 0·799, n.s.).

Taking all grafts together, patency was adversely affected by small veins of <4 mm internal diameter ($P<0·005$), long grafts with below knee, as compared to above knee, distal anastomosis ($P<0·01$), mean volume of blood flow in the grafts of less than 200 ml/min following injection of papaverine 30 mg into the lumen ($P<0·001$) and poor run-off with one or no tibial vessels visible on pre-operative angiograms as compared with two or three patent vessels ($P<0·05$). However, comparison between the patency of reversed and *in situ* grafts for each of these high risk subgroups, i.e. small veins, long grafts, low volume blood flow and poor run-off, showed no advantage for either operation. In all cases the reversed vein grafts had slightly higher patency rates but the differences were not statistically significant.

The following factors did not have any effect on the patency rates of any of the grafts. Severity of disease as indicated by presenting symptoms and pre-operative ankle:arm pressure index, the presence of diabetes and the addition of a concomitant procedure to improve inflow.

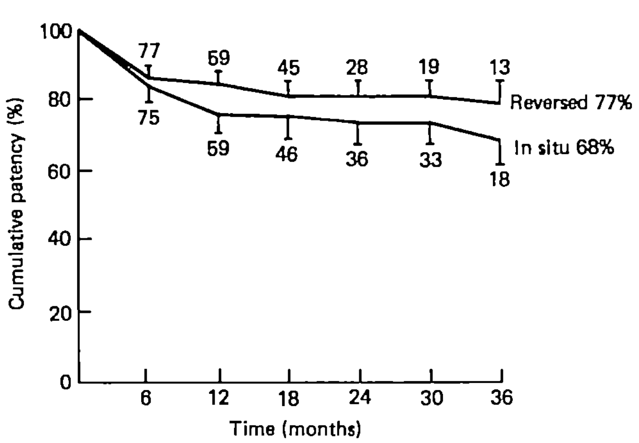

Figure 1 *Comparison between the cumulative patency rates of reversed and* in situ *saphenous vein grafts* (n = 200) *over a 3 year period. The number of grafts available for study at each interval is shown, and the s.e.m. at each point is represented by the vertical bars. Lee–Desu statistic = 0·799, n.s.*

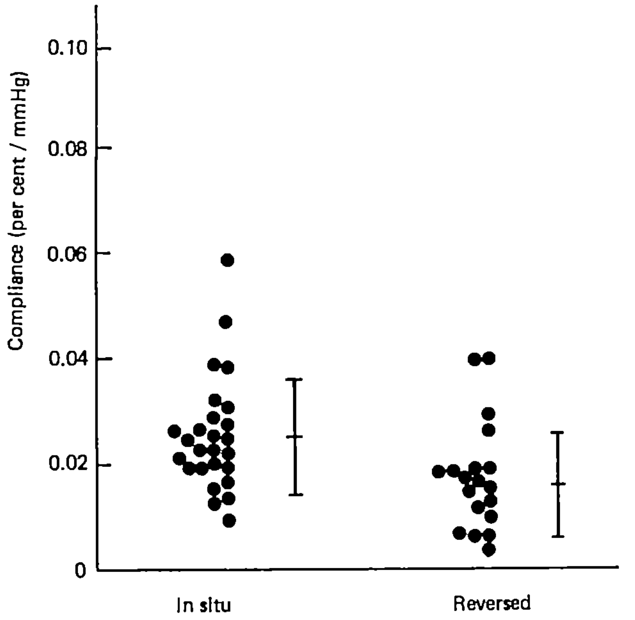

Figure 2 *Comparison between the compliance of* in situ (n = 26) *and reversed saphenous* (n = 19) *vein grafts. The mean* (in situ, *0·025; reversed, 0·016*) *and s.d. of each group is shown. Student's* t = *2·428,* P < *0·02*

Fibrous stricture formation

A review of intravenous digital subtraction angiograms revealed fibrous strictures in 10 of 34 reversed vein grafts (29 per cent) and 13 of 45 *in situ* vein grafts (29 per cent).

Graft compliance (Figure 2)

The mean compliance of 26 *in situ* vein grafts was 0·024 ± 0·01 per cent/mmHg (±s.d.) and that of 19 reversed vein grafts was 0·017 ± 0·01 per cent/mmHg (±s.d.). The difference between the means was just statistically significant ($t = 2·43$, $P < 0·02$) indicating that the *in situ* vein grafts were on average slightly more compliant than reversed vein grafts; however, both grafts were less compliant than normal superficial femoral arteries assessed by the same technique.

Discussion

The results of this study to date do not give support to claims that in femoropopliteal bypass surgery the performance of *in situ* vein grafts is superior to that of reversed vein grafts. In terms of patency the trend was, if anything, in favour of the reversed operation but there was no difference in performance of any statistical significance. The two operations were also very similar in respect of ease of surgery, but more of the veins which were allocated to the reversed operation were rejected on the grounds that they were too small, than those allocated to the *in situ* operation. This finding confirms that it is possible to utilize more small veins by the *in situ* technique[7], but an analysis of the patency of such grafts indicates that the outcome is likely to be disappointing. Veins of small size had an adverse influence on the outcome of operation when either reversed or *in situ* grafts were employed and this finding indicates that the results of both procedures could be improved by a more critical policy with regards to the rejection of veins on the basis of their small size. The question remains unanswered, however, as to what is the minimum size of vein below which the results are worse than can be expected from the best prosthetic substitutes.

Longer grafts to the infrageniculate popliteal artery carried a significantly poorer chance of long term patency than above-knee grafts but the results showed that long *in situ* grafts fared no better than long reversed grafts despite previous claims to the contrary[7]. When there is a marked change in diameter between the donor and recipient artery, as for example in the case of a femorotibial bypass, then the natural taper of the *in situ* graft undoubtedly represents an advantage, and this therefore remains the preferred method in this situation. If it is true that *in situ* vein grafts retain an intact endothelium and the facility to secrete plasminogen activator substances then it might be expected that, as a result of decreased thrombogenicity, they would perform more successfully in situations where the run-off is poor and the velocity of blood flow in the graft is low. In fact *in situ* grafts did not perform any better than reversed vein grafts in the presence of low flow rates as measured at operation or when the run-off was poor owing to disease in the tibial vessels, and if any difference in thrombogenicity of the two grafts does exist it would seem to be of little importance in the context of femoropopliteal bypass operations.

The small but significant difference in compliance between the two types of graft is of interest and indicates that the *in situ* technique probably does in fact favour the retention of some wall elasticity. This may be the result of preserved viability or due to some other difference in handling and preparation of the two types of graft. Previous studies have shown that the compliance of femoral arteries in clinically disease-free men decreases with age from 0·059 per cent/mmHg in those aged 35 years or under to 0·042 per cent/mmHg in those aged 35–60 years and 0·0315 per cent/mmHg in those over 60 years of age[14]. It is apparent therefore that with mean levels of 0·024 per cent/mmHg for the *in situ* grafts and 0·017 per cent/mmHg for the reversed grafts, both types of graft are considerably less compliant than the ideal. The relevance of the difference between them remains uncertain at this stage but there has been no demonstrable effect on patency rates to date, and it seems unlikely in view of the apparent trends that longer follow-up will reveal any clinical benefit associated with the marginally better compliance of the *in situ* grafts.

Fibrous strictures were common to both types of graft. Most were found close to the anastomoses and exploration of this type of lesion has shown changes resembling subintimal hyperplasia. However, strictures were also observed in the central portion of the grafts and the aetiology of these remains obscure. The finding of an equal incidence of these lesions in the reversed and *in situ* grafts indicates that valve trauma or incomplete rupture of a cusp by the valvulotome is probably not the main cause in the *in situ* grafts. It is not known whether the presence of these strictures represents a serious risk to long term patency or whether in the absence of symptoms an attempt should be made to correct them by balloon angioplasty or open operation but we hope further follow-up of this series will help to answer these questions.

In conclusion, the results of this trial to date indicate that the *in situ* and reversed vein graft operations are equally effective for femoropopliteal bypass and the choice of procedure should therefore remain a matter of personal preference on the part of the surgeon.

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Intraluminal long saphenous vein stripping: a technique minimizing perivenous tissue trauma

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The technique of intraluminal stripping of the long saphenous vein in the patient with varicosities was first described by Keller[1] in 1905, with further modification by Babcock[2] and later by van der Stricht[3].

We describe a modification of Keller's original technique for intraluminal stripping of the long saphenous vein to above or just below the knee which carries the advantages of excision of this segment whilst minimizing the disadvantages of postoperative haematoma and saphenous nerve damage.

Method

Standard operative technique for long saphenous vein stripping involves the passage of Myer's stripper usually from above following flush saphenofemoral ligation. The stripper end is secured with an acorn ($\frac{1}{4}$, $\frac{3}{8}$ or $\frac{1}{2}$ inch diameter) which inevitably causes substantial tissue damage. Our technique involving stripping without an acorn is described below.

The saphenofemoral ligation is carried out in the usual way. A conventional Myer's stripper wire is passed down the long saphenous vein to around the knee. It is usually possible to negotiate the valves without difficulty. The point of the wire is then located by palpation and a cut-down through a 0·5–0·75 cm incision is performed. The vein is identified and a small venotomy made through which the lower end of the stripper is pushed. It is then drawn through until the upper end is near the upper end of the vein in the groin incision. A very firm ligature is then placed around the uppermost part of the vein to secure it to the stripper wire. Traction is then applied to the lower end of the stripper wire thus inverting the upper end of the vein with the stripper wire into the lumen. Further traction on the lower end of the stripper wire then avulses the vein which is drawn through the venotomy with the intimal surface now outwards. When avulsion is complete a clamp is placed below the venotomy. The upper part can be excised and the distal end ligated. The skin incision is closed with a single intracuticular 5/0 polyglycolic acid suture. This stripping procedure can be carried out early in the operation as stripping track bleeding does not occur. The remaining technique is conventional: calf veins are dealt with by stab avulsions and wounds are closed with Steri-Strip or intracuticular sutures.

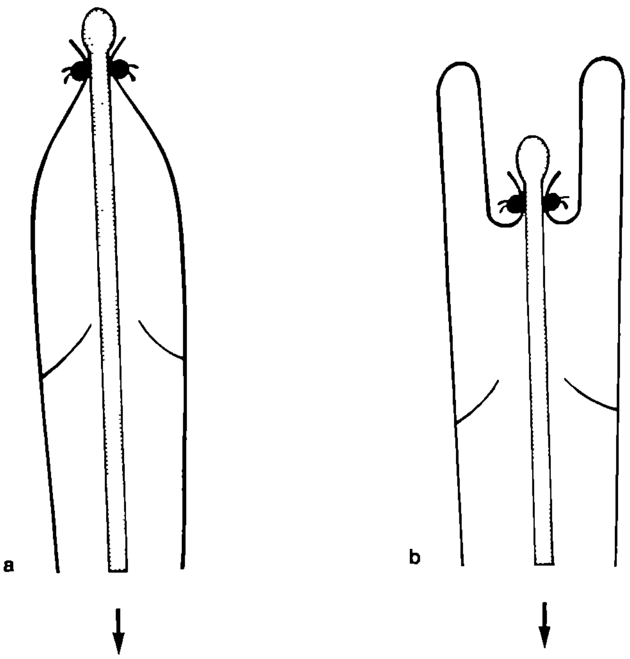

Figure 1 *The intraluminal technique*

Discussion

The technique described removes the long saphenous vein segment by intraluminal intussusception (*Figures 1a* and *b*). The traumatized area is only the diameter of the vein itself. We have used this technique in all our patients with long saphenous vein incompetence and have found it entirely satisfactory with minimal postoperative morbidity. The technique is simple and has distinct advantages over conventional stripping in reducing postoperative pain and haematoma formation.

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Secondary arterio-enteric fistulae: a surgical challenge

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Ten cases of secondary arterio-enteric fistulae are described. There were nine graft enteric fistulae and one fistula involving the aortic suture line following elective resection of an infected graft. Only four of the patients initially received prophylactic antibiotics (single dose) at the original aortic reconstruction, and the vascular suture line had only been protected in two. Eight patients presented with bleeding and two with groin abscesses. One patient died before operation. Graft resection was undertaken in all patients and organisms were grown from six of eight grafts cultured. No patient died during operation but one died after 3 days. Axillofemoral bypass grafts were constructed in seven patients (four immediately after resection of prosthetic grafts and three within 4 days of operation). Only three of the eight patients who survived operation are still alive; two died of a ruptured aorta and one from a recurrent fistula. Two patients died of other causes. Four of five axillofemoral grafts in surviving patients subsequently occluded.

Keywords: Arterio-enteric fistulae

A primary (spontaneous) fistula between an abdominal aortic aneurysm and the duodenum was first described by Sir Astley Cooper in 1825[1], and since then fewer than 200 cases have been reported[2]. Secondary (postoperative) fistulae are a complication of intra-abdominal aortic grafts. The first report of a secondary fistula was made by Brock in 1953[3]. He described a fistula between the duodenum and a false aneurysm arising from the left iliac artery anastomosis occurring one year after insertion of an aortic homograft. Three years later Claytor reported a fistula associated with a prosthetic graft[4]. With the expansion in aortic reconstructive surgery over the last three decades, there has been an increasing number of reports of secondary fistulae, indicating that this potentially fatal complication should no longer be considered a rarity.

We present our experience of 10 patients with secondary arterio-enteric fistulae. Despite good early results, recurrent fistulation, rupture of vascular suture lines and occlusion of extra-anatomic bypass grafts was associated with a very high subsequent morbidity and mortality.

Patients and methods

Ten patients with secondary arterio-enteric fistulae presenting to the Royal United Hospital, Bath, between 1980 and 1984 were reviewed. There were three women and seven men of mean age 64 years (range 49–84).

All the patients had undergone aortic surgery between 2 and 7 years previously. Two aortic aneurysms had been repaired electively using Dacron inlay grafts. The grafts had been covered with the aneurysm sac and in one case a Dacron cuff had been placed around the proximal anastomosis. In eight patients with occlusive disease Dacron grafts had been inserted by onlay technique. There was no record of any graft covering procedures in the original operation notes.

Four of the ten patients had received perioperative single dose antibiotic prophylaxis with lincomycin and tobramycin. Postoperative infective episodes had developed in three patients.

Presentation and diagnosis

Eight patients presented with upper gastrointestinal haemorrhage. Two patients reported chronic intermittent melaena, while the remainder gave a history of acute bleeding. One patient had recently presented with lower limb ischaemia due to graft occlusion.

Two patients presented with unilateral groin abscesses and an infected, occluded graft. In both cases the femoral anastomoses were disconnected, the graft limb ligated and antibiotic therapy instituted. One patient had a haematemesis 2 days later and underwent immediate operation for an aortoduodenal fistula. In the other case, elective graft resection and aortic thrombectomy were performed 3 weeks later. Nine days after operation the patient bled from an aortoduodenal fistula.

Gastroscopy was performed in six patients to exclude other upper gastrointestinal pathology. An aortogram was undertaken in one case and demonstrated a pseudo-aneurysm at the aortic anastomosis. Three patients underwent surgery on clinical grounds alone. The final patient died before any investigations were undertaken.

Site of fistula (Table 1)

There were seven proximal fistulae, two distal fistulae and one ilio-appendicular fistula. A vascular suture line was involved in each case.

Operations (Table 1)

Proximal aortic control was first achieved before dissecting out the fistula. The bowel was repaired, the graft removed, and an aortic thrombectomy performed. Vascular suture lines were carefully covered with omentum and peritoneum, and perioperative antibiotics given in all cases.

In four patients who had previously undergone operation for non-critical ischaemia, no immediate reconstruction was performed; three of these required a delayed axillobifemoral bypass graft. Four patients had immediate axillobifemoral grafts. In all cases an 8 mm knitted double velour Dacron graft was used. One young patient, who previously had an aneurysm repaired, had no overt evidence of infection, and a new Dacron bifurcation graft was inserted.

Graft infection (Table 1)

At operation obvious graft infection with free pus was present in five patients and organisms were grown from six of the eight grafts cultured. Histology of the appendix in the patient with an ilio-appendicular fistula showed resolving acute appendicitis.

Results

One patient died during induction of anaesthesia, and another from multisystem failure 3 days after operation. Two patients died of a ruptured aorta: one 6 weeks postoperatively and the other, with a replacement aortic graft, 2 years later.

Two of the three patients who received delayed axillobifemoral grafts developed ischaemic damage to the anterior tibial compartment; one with tissue necrosis, the other with ischaemic neuritis and foot drop. The first subsequently came to amputation for progressive ischaemia and has since died of carcinoma of the prostate. The second developed a

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Table 1 *Clinical features of 10 patients with secondary arterio-enteric fistulae*

Patient	Original graft	Fistula site	Graft culture	Operation (all aortic grafts removed)	Axillobifemoral graft	Outcome
1	Onlay	Aortoduodenal	—	Aortic repair	No	Alive Claudicating at 300 yards
2	Inlay	Aortojejunal	*Candida*	New graft	No	Dead Ruptured aorta (2 years)
3	Onlay	Aortoduodenal	Coliforms, α-haemolytic streptococci	(Elective graft removed previously) Aorta ligated, oversewn and covered with omentum	Immediate	Dead. Occluded bypass graft (8 weeks) Aortocolonic fistula (12 weeks)
4	Onlay	Ilio-enteric	Coliforms, non-haemolytic streptococci	Aortic repair	Immediate	Dead (3 days) Multisystem failure
5	Inlay	Ilio-enteric	Nil	Aortic repair	Immediate	Dead. Occluded bypass graft, myocardial infarction (4 months)
6	Onlay	Aortoduodenal	Coliforms, non-haemolytic streptococci	Aortic repair	Delayed	Dead Ruptured aorta (6 weeks)
7	Onlay	Aortoduodenal	Coliforms, non-haemolytic streptococci, *Bacteroides fragilis*	Aortic repair	Delayed	Alive. Occluded bypass graft removed. New bypass graft (4 months). Foot drop
8	Onlay	Aortoduodenal	Nil	Aortic repair	Delayed	Dead. Amputation (6 months). Carcinoma of prostate (3 years)
9	Onlay	Ilio-appendicular	β-haemolytic streptococci	Proximal aorta and external iliacs oversewn	Immediate	Alive. Infected bypass graft removed. New bypass graft (4 months)
10	Onlay	Aortoduodenal	—	Nil	—	Died pre-operatively

blocked graft after 4 months which was successfully replaced, but she now has a carcinoma of the lung.

In three patients who had immediate axillobifemoral grafts, the bypass became occluded within 4 months of operation. The first developed an aortocolonic fistula one month after bypass thrombectomy and died postoperatively of renal failure; the second had a new axillobifemoral graft and remains well. The third patient died of a myocardial infarct after unsuccessful bypass graft thrombectomy.

The final patient who had her fistula closed and the graft removed, but no reconstruction, remains alive and well 4 years later. However, she claudicates at 300 yards.

Discussion

The development of a secondary fistula is a direct complication of aortic surgery. Secondary fistulae are reported to occur in approximately 0·5 to 4·0 per cent of all patients after aortic grafting procedures[5–8]. The incidence is higher after emergency aneurysm repair than elective operation[6,9]. Elliott, in a personal series of 2085 aortic reconstructions, found an overall incidence of 0·6 per cent. However, after emergency aortic aneurysm repair, the incidence was 1·7 per cent[6]. Likewise, Busuttil *et al.*[9] reported an incidence of 1·7 per cent for ruptured aneurysm, 0·17 per cent for elective aneurysm repair and 0·2 per cent for elective aortic cases. Approximately 75 per cent of fistulae communicate with the duodenum and 15 per cent with the small bowel[6,10–12]. Involvement of the colon and appendix is rare.

Secondary fistulae may involve the prosthetic vascular suture line, the body of the graft or an arterial suture line following removal of an infected graft. Bunt[12,13] differentiated between fistulae involving the prosthetic vascular suture line (graft enteric fistulae; GEF) and the less common graft enteric erosion (GEE) in which the graft body alone is affected. In the latter, previously termed 'para-prosthetic fistulae', the lumen of the bowel and prosthesis communicate via the interstices of the prosthetic graft[13]. Patients with GEE usually have a localized infection and no direct communication with the arterial lumen; as a result they do not present with the sudden massive haemorrhage characteristic of GEF[12,14]. Rather, they present with sepsis, haematochezia, melaena or anaemia. Graft enteric erosion is a mechanical erosion of the bowel by the pulsatile graft[12], whereas infection in addition to mechanical forces is likely to be of major importance in GEF[9,11,12,14]. However, Eastcott[28] advised that in some cases of GEF mechanical forces alone could result in tissue breakdown and fistula formation independent of any infective process.

The most likely cause of graft infection is local contamination at the time of reconstruction[14]. Predisposing factors include multiple vascular procedures, groin incisions, wound complications, emergency aneurysm repair and technical difficulties[13]. This series supports the importance of infection in the development of fistulae; two-thirds of the patients had overt sepsis at operation and in only two did graft cultures fail to grow organisms. The development of an ilio-appendicular fistula secondary to acute appendicitis indicates that patients with prosthetic grafts who later develop an acute intra-abdominal inflammatory process are at risk.

Identification of the aetiological factors has important implications for prevention and treatment. Strict asepsis must be observed during aortic reconstructive surgery, and the operation abandoned if the bowel is perforated[11]. Minimal mobilization of the duodenum is recommended to prevent any damage to the bowel wall[6]. Prophylactic broad spectrum antibiotics should be given pre-operatively and continued until all sources of infection are removed[15,16]. Careful surgical technique, using correct graft size and tension and avoiding arterial silk sutures, is no doubt important in reducing the likelihood of mechanical erosion of bowel by the prosthesis. Furthermore, it is most important to protect the graft and all suture lines from bowel. This can be achieved by using Dacron cuffs, aneurysm sac or omentum and by careful reperitonealization. In this series none of the onlay grafts had been covered.

Clinical suspicion is the mainstay of diagnosis. Patients with an aortic graft or previously resected infected graft who present with gastrointestinal haemorrhage, abdominal pain or sepsis should be considered as having a fistula until proved otherwise[11,17,18]. Warning or herald bleeds are usual due to the stop-cock effect of thrombus in the fistula tract. As in this series, there is usually at least 6 h between initial bleed and operation or death; occasionally days or even weeks elapse[19].

Investigation must not delay timely operation before the onset of massive fatal haemorrhage. Several reports have described the value of oesophagogastroduodenoscopy to establish a pre-operative diagnosis of GEF or GEE[20–22]. Abnormal findings at endoscopy include an extra-enteric pulsatile mass, punctate ulceration of the distal duodenum and even visualization of the intraluminal graft. However, endoscopy can be hazardous and may result in massive haemorrhage[23], and should be performed in the operating theatre with the patient prepared for surgery. Endoscopy is also useful to exclude peptic ulceration and oesophageal varices. Up to 23 per cent of patients with abdominal aortic aneurysms have associated peptic ulceration[24]. Arteriography may show a pseudo-aneurysm or a nipple of contrast at the aortic suture line[23,25]. Computerized tomography may demonstrate pseudo-aneurysm formation and gallium scanning may indicate an infected graft. Likewise, the presence of lower limb cutaneous septic emboli[26], a petechial rash[27], and positive femoral arterial blood cultures with negative blood cultures from arm veins[6] may aid diagnosis.

Two main operative strategies have been used for the treatment of secondary fistulae, either direct repair of bowel and vascular suture line (or graft body) or graft resection combined in most cases with a lower limb revascularization procedure. Eastcott[28] advised that direct repair or segmental graft resection should be considered in patients without apparent pre-operative and intra-operative infection as determined by pre-operative femoral artery blood cultures and Gram stains of tissue samples at operation. Cranston and Vowles[29] reported a patient who underwent successful direct repair of an aortoduodenal fistula and who several years later developed an aortocolonic fistula which was again successfully repaired by the direct approach. The advantage of direct repair is that it is a relatively quick procedure and if successful is not associated with a long period of lower limb ischaemia. However, direct repair may be associated with a mortality approaching 90 per cent[12]. In addition, recurrent fistulation and pseudo-aneurysm formation also make simple repair hazardous. Infection, even if unproven, is invariably present and therefore most surgeons now favour total graft excision, local debridement of infected tissue with drainage and possibly antibiotic irrigation. The aorta should be closed carefully and suture lines protected with either omentum[30], prevertebral fascia[31], or a jejunal patch[32].

Graft excision usually necessitates a lower limb revascularization procedure. In patients treated solely by graft excision without revascularization there is an unacceptably high mortality of nearly 75 per cent[12]. Occasionally, as in one of our patients who had previously had an onlay graft for occlusive disease, lower limb revascularization may not be essential.

Several techniques are described to re-establish lower limb perfusion after graft excision. Prosthetic graft replacement *in situ* has met with some success but the overall mortality is nearly 60 per cent[12]. The occurrence of complications of continuing infection, such as recurrent fistulation and aortic dehiscence (as occurred in our case treated by this method), have made this an unsatisfactory procedure. In 1979 Ehrenfeld *et al.*[33] suggested using autogenous tissues—either vein or endarterectomized artery. Although considerable technical problems exist in obtaining suitable autogenous vessels, this approach has met with success. Furthermore, the use of autogenous tissues obviates the need to remove all prosthetic material in the presence of infection and re-establishes lower limb perfusion, and reduces the likelihood of aortic disruption as aortic continuity is re-established[13]. This approach is supported by Seeger *et al.*[34]. In contrast to these favourable reports others claim that autogenous grafts are prone to disruption in the presence of marked infection[35–37].

In recent years prosthetic extra-anatomic bypass grafts, usually axillofemoral, have become the most widely accepted method to re-establish lower limb perfusion. Bunt[12] reported an overall mortality of 38 per cent for this treatment. If possible the remote bypass should be inserted before aortic graft excision, as this strategy carries a mortality of 17 per cent compared with 53 per cent when the bypass graft is inserted after aortic graft excision[14]. Although remote bypass and graft excision may of necessity have to be undertaken at operation for massive bleeding, Trout[14] suggested that if bleeding is modest and an erosion or fistula is found at laparotomy, a local repair can be performed with immediate remote bypass grafting. The infected graft can then be removed at a later date.

In this series, seven patients underwent remote bypass grafting after graft excision. Only one patient died in the early postoperative period, which is at variance with the poor results reported by Trout[14]. Remote bypass grafting after excision of the graft was associated with distal ischaemic problems in two patients. However, in these two cases the bypass graft had been inserted more than 24 h after graft excision. In the patients who received immediate remote bypass grafts, the problems were of occlusion and infection, presumably acquired at the time of construction.

Despite the good immediate survival of patients in this series, the long-term results have been disappointing. Late dehiscence of the vascular anastomosis implies a continued infective process; possibly these patients should receive continuous low dose prophylactic antibiotics. Aortic thrombectomy with aortic repair which was undertaken in this series may leave a potential source of fistulation, and double ligation and double oversewing of the aorta in one case did not prevent this happening.

It would appear that graft excision with prior fashioning of a remote bypass graft or the use of autogenous grafts *in situ* may offer the best chance of survival for patients with graft enteric fistulae. However, prevention of this complication is paramount and every precaution must be taken at the original operation to prevent the subsequent development of a fistula. This series highlights the importance of antibiotic prophylaxis and adequate retroperitonealization and protection of the graft.

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Transcranial Doppler assessment of cerebral collateral during carotid endarterectomy

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Sixteen patients (mean age 59 ± 9 years) who were to undergo carotid endarterectomy were examined pre- and peroperatively using pulsed Doppler-shifted ultrasound; blood velocities in the middle cerebral artery were measured before and during common carotid compression in the conscious patient, and before and during measurement of carotid stump pressures at surgery in the anaesthetized patient. Measurements at endarterectomy showed a significant difference in middle cerebral artery blood velocities from patients with stump pressures of greater and less than 50 mmHg ($t = 4{\cdot}0$, $P < 0{\cdot}005$). A threshold of 10 cm s^{-1} distinguished between stump pressures of greater and less than 50 mmHg in 15 of the 16 patients. Pre-operative blood velocity measurements during carotid compression did not correlate with those taken peroperatively at carotid clamping.

Keywords: Middle cerebral artery, Doppler ultrasound, blood flow

Several non-invasive techniques have been used for assessment of extracranial cerebrovascular disease[1–4]. Investigation of the cerebral collateral circulation has received less attention; such methods as electro-encephalography[5,6], xenon inhalation[7,8] and carotid stump pressures[9,10] are used but can provide unreliable results and are either invasive or difficult to perform continuously. Carotid stump pressures have been used most frequently and a stump pressure >25 mmHg has been reported to indicate a good cerebral collateral circulation[11]. However, general anaesthesia has a variable effect on cerebral blood flow and Boysen[12] reported that only stump pressures >50 mmHg indicate good cerebral collateral circulation.

Aaslid and his colleagues[13] first reported use of transcranial pulsed Doppler ultrasound to monitor blood velocities in basal cerebral arteries and we have since used this non-invasive technique in combination with common carotid compression to assess the functional potential of the circle of Willis[14]. It has also recently been shown that Doppler-shifted frequencies from the middle cerebral artery closely follow changes in cerebral blood flow[15,16].

In this paper we report a method using transcranial pulsed Doppler ultrasound and spectral analysis to provide a numerate assessment of cerebral collateral blood supply to the middle cerebral artery during clamping of the common carotid artery at carotid endarterectomy.

Patients and methods

Patients

Sixteen patients (14 men and 2 women) of mean age 59 years (±9, range 42–72) were investigated, all of whom had suffered from transient ischaemic attacks and subsequently underwent carotid angiography.

Apparatus

A 2 MHz pulsed Doppler ultrasound velocimeter (Alfred, Vingmed, Norway) and an 8 MHz continuous wave Doppler velocimeter (Sonicaid, BV380) were used. Backscattered ultrasound signals were output from the phase sensitive quadrature detectors and analysed into positive and negative Doppler-shifts which were recorded on the separate tracks of a stereo cassette tape. Further processing was performed by a two-channel spectral analyser (Doptek, Chichester, Sussex, UK), with the signals displayed in sonagram format (*Figure 1*). A BBC B microcomputer (Acorn) which was interfaced to the analyser and controlled by an optical pad (Summamouse, Summagraphics) was used to analyse the signals. Suitable software enabled calculation of the intensity weighted mean Doppler frequency per spectral sweep (every 5 ms), which was then time-averaged over each cardiac cycle[17].

Internal carotid artery stump pressures were measured using a 21-gauge needle connected to a fluid-filled pressure transducer (Statham) and chart recorder.

Pre-operative measurements. A 2 MHz pulsed Doppler transducer was placed on the side of the head just superior to the zygomatic arch and blood velocity signals were recorded from the ipsilateral middle cerebral artery[14]. The response of the middle cerebral artery to ipsilateral common carotid compression was determined. Common carotid compression was performed low in the neck for five cardiac cycles with digital pressure being both applied and released slowly. The effectiveness of compression was assessed by monitoring blood velocities in the ipsilateral superficial temporal artery with an 8 MHz continuous wave Doppler velocimeter. Compression responses were taken at the point when the ipsilateral superficial temporal artery pulse was obliterated. The percentage reduction in middle cerebral artery time-averaged blood velocities was calculated from data recorded before and during ipsilateral common carotid compression.

Peroperative measurements. Middle cerebral artery blood velocities from the side of the carotid endarterectomy were monitored continuously before and during clamping of the ipsilateral common carotid artery. The internal carotid artery stump pressure was measured in all patients before placement of a Javid shunt. The common and external carotid arteries were temporarily clamped and a 21-gauge needle then inserted into the common carotid artery just proximal to the carotid bifurcation, the mean pressure thus recorded being the stump pressure.

Analysis

The mean blood velocity in the middle cerebral artery was calculated by averaging the intensity-weighted mean Doppler-shifted frequency for each spectral sweep over three consecutive cardiac cycles. This time-averaged Doppler frequency could be related directly to blood flow as the vessel diameter and transducer/vessel orientation were assumed to remain constant[16]. The measured Doppler-shifted frequency was converted to blood velocity by taking the ultrasound propagation velocity as 1540 m s^{-1} and the ultrasound beam to be in line with the artery[18], thereby 1 kHz of Doppler-shifted frequency was equivalent to a blood velocity of 38·5 cm s^{-1}. Three consecutive cardiac cycles obtained from each patient both before and during common carotid compression were analysed. The mean compression value was expressed as a percentage of the resting value. Statistical analysis of the blood velocity data was performed by linear regression and Student's *t* test for unpaired values.

Results

The relationship between internal carotid stump pressure at operation and the simultaneously obtained value of ipsilateral

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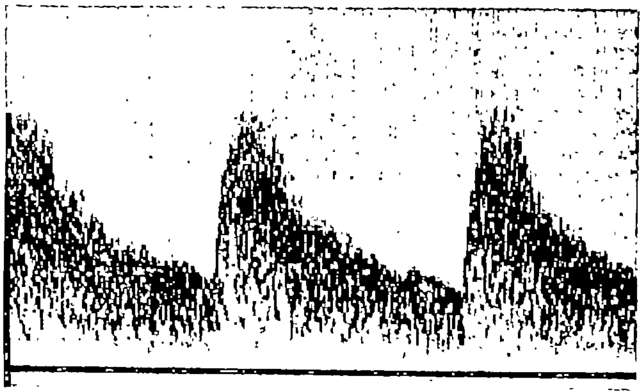

Figure 1 *Sonograms from the middle cerebral artery of a healthy young volunteer. Doppler-shifted frequency is on the ordinate, time on the abscissa and the darkness of the trace is related to the amplitude of the signal*

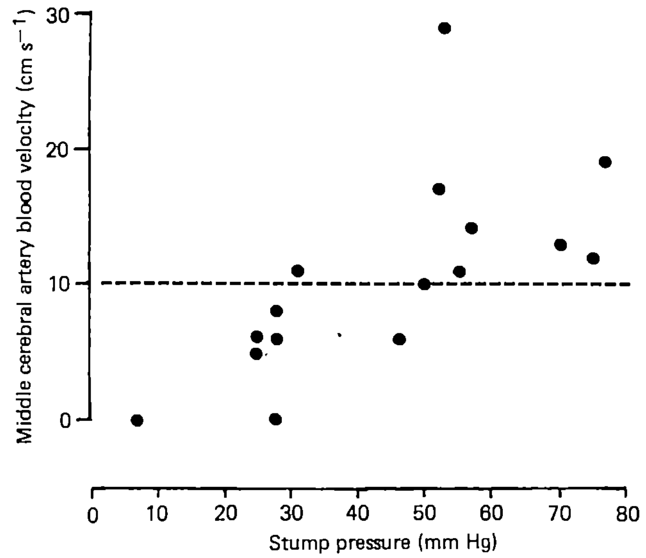

Figure 2 *Relationship between internal carotid artery stump pressures and simultaneously measured ipsilateral middle cerebral artery time-averaged blood velocities obtained during the 16 carotid endarterectomies*

middle cerebral artery blood velocity ('clamp value') is shown in *Figure 2*. A threshold of 10 cm s^{-1} in middle cerebral artery blood velocity identified internal carotid stump pressures greater or less than 50 mmHg in 15 of the 16 patients, the difference between the two groups being significant ($t=4·0$, $P<0·005$). Regression analysis demonstrated a linear relationship between these two parameters ($r=0·67$, $P<0·005$).

Figure 3 shows the relationship between stump pressure and the simultaneously measured middle cerebral artery blood velocity expressed as a percentage of the resting levels. A threshold of 50 per cent reduction in middle cerebral artery blood velocity correctly identified whether the stump pressure was greater or less than 50 mmHg in 12 of the 16 patients; the difference between these groups was significant ($t=5·1$, $P<0·005$), although the relationship between the two parameters was not linear ($r=0·54$, n.s.).

Figure 4 shows the values of middle cerebral artery blood velocity measured pre-operatively (at rest and during digital compression of the ipsilateral common carotid artery) and peroperatively (at rest and during ipsilateral carotid clamping). There was no linear relationship between the pre- and peroperative blood velocity data ($r=0·27$, n.s.).

One postoperative stroke developed, but this was not associated with the side of the operation. The patient had bilateral internal carotid stenoses (≈90 per cent) and was only symptomatic from the stenosis on the side of the endarterectomy.

Discussion

Middle cerebral artery blood velocity levels during clamping of the ipsilateral common carotid artery and the simultaneous value of stump pressures showed that a threshold of 10 cm s^{-1} in middle cerebral artery blood velocity distinguished between stump pressures greater and less than 50 mmHg. This threshold could therefore be used to differentiate between good and poor cerebral collateral blood supplies as indicated by carotid stump pressures.

Only one patient had a stump pressure <25 mmHg. This patient and a further five who had stump pressures close to 25 mmHg (<30 mmHg) had low 'clamp values' of middle cerebral artery blood velocity (0–8 cm s^{-1}; *Figure 2*). As different

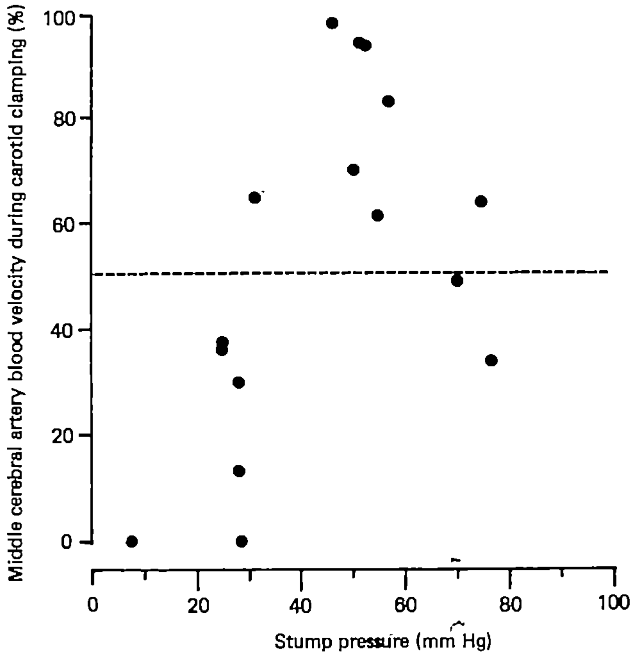

Figure 3 *Relationship between internal carotid artery stump pressures and simultaneously measured ipsilateral middle cerebral artery blood velocities, expressed as a percentage of pre-clamp values (100 per cent = no change in blood flow during clamping), obtained during the 16 carotid endarterectomies*

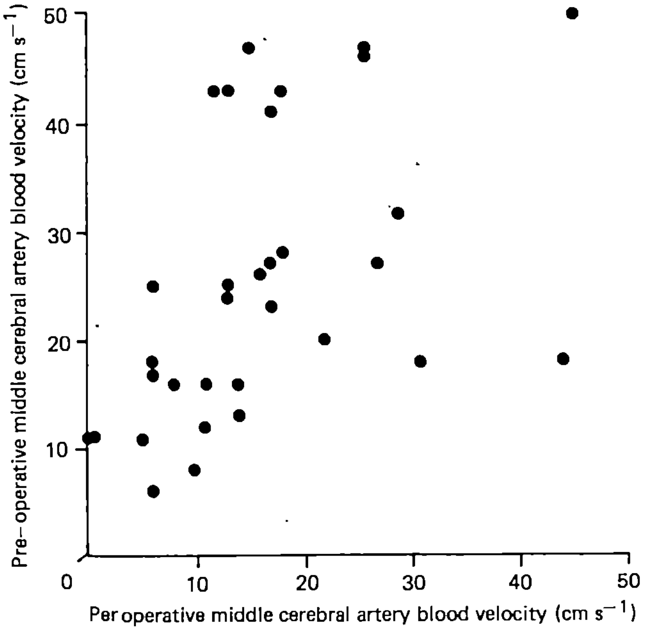

Figure 4 *Relationship between pre- and peroperative values of middle cerebral artery blood velocity at rest and during ipsilateral carotid clamping for the 16 patients*

thresholds for internal carotid stump pressure (25 and 50 mmHg) have been suggested for indicating good cerebral collateral blood supply[11,12], measurements within this range are controversial. The ultrasound assessment described may be particularly useful for this group since the level of middle cerebral artery blood velocity could indicate poor perfusion which is not detected by a threshold in stump pressure of 25 mmHg. Such a discrepancy was observed in the one patient who had a postoperative stroke. Bilateral severe internal carotid artery stenoses were present and the stump pressure was 28 mmHg whilst the middle cerebral artery clamp velocity was zero.

Measurements obtained peroperatively were analysed to determine if they could be used to define thresholds for data obtained in the conscious individual. However, middle cerebral artery blood velocity levels recorded in conscious patients were not linearly related to those measured in the same patients under general anaesthesia (*Figure 4*). Incomplete common carotid compression in the awake subject is one explanation for these differences, but digital compression in all the conscious patients was sufficient to stop superficial temporal blood flow. An additional explanation is the effect of general anaesthesia on the cerebral circulation; anaesthesia was induced using an opiate and maintained by an inhaled anaesthetic, a combination which can have opposing effects on cerebral blood flow[19].

Non-invasive transcranial measurement of middle cerebral artery blood velocities provides a numerate assessment of the cerebral collateral circulation to the middle cerebral artery territory in the anaesthetized patient. The assessment may be performed throughout surgery with no inconvenience to surgeon or anaesthetist and the instantaneous display of Doppler signals on a spectral analyser can alert a surgeon to sudden decreases in middle cerebral artery blood velocity level[18]. When shunting is used selectively, the transcranial measurement could be of particular value to determine those patients who would most benefit from shunting. Prospective assessment of cerebral collateral supply is required to determine the relative importance of middle cerebral artery blood velocity and stump pressures. Validation of measurements obtained in the conscious subject however awaits development of a suitable stress test.

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Assessment of perfusion in postoperative patients using tissue oxygen measurements

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Subcutaneous tissue oxygen tension was measured as an index of perfusion in 44 postoperative patients. Hypoperfusion was defined as suboptimal tissue oxygen tension unresponsive to increased inspired oxygen but becoming responsive after increased fluid infusion. Twelve of thirty patients who underwent major abdominal and flank operations were found to be suboptimally perfused by this definition despite adequate fluid maintenance according to standard clinical criteria including urine output. Apparently, a significant number of postoperative abdominal surgery patients are not optimally perfused, and this state is not recognized by the present clinical criteria. Tissue oximetry may be a useful objective method of assessing tissue perfusion.

Keywords: Tissue oxygen tension, perfusion, rehydration

Peripheral perfusion in operative patients, important for many reasons, is particularly pertinent to healing and resistance to infection[1–4]. Most surgeons judge peripheral perfusion by blood pressure, pulse rate and urine output. This study was designed to determine the frequency with which surgeons encounter patients with depressed peripheral tissue perfusion and simultaneously adequate urine output. Direct measurement of subcutaneous tissue oxygen tension was used as an index of perfusion and was found to be considerably more informative than urine output.

Patients and methods

For the purposes of this investigation hypoperfusion was defined by the following criteria: low subcutaneous (tissue) P_{O_2} during air-breathing; failure of tissue P_{O_2} to rise significantly in response to increased concentrations of inspired oxygen; subsequent significant response of tissue P_{O_2} to breathing oxygen after rapid fluid administration. 'Adequate' urine output was defined as 50 ml/h or more.

Tissue oxygen tension was measured in 44 patients after 46 surgical procedures, all but one of which were elective. Patients admitted to the study were under the personal observation of the surgeon authors and, with one exception, were solicited pre-operatively if they could be expected to remain in hospital long enough to complete the study. No volunteer nor any data was excluded for any reason. Pertinent demographic and background information is presented in *Tables 1, 2* and *3*. Except as specified, standard clinical procedures were used throughout. All studies were done between October 1982 and July 1983. This study was approved by the Human Research Committee at the University of California, San Francisco, USA. Informed consent and written permission were obtained from all participants.

Oximetry was performed as has been previously described[5]. At the end of the operation, when the patient was still under general anaesthesia, a gas-sterilized Silastic® catheter (1 mm outer diameter, 0·8 mm inner diameter, 15 cm long) was introduced subcutaneously into the lateral upper arm through an 18 gauge spinal needle. The entrance and exit points were 7 cm apart. One end of the tube, ending in a 22 gauge angiocatheter (Abbocath T®), was sutured to the skin. The needle end was cut 1·5 cm from the skin (*Figure 1*). A single piece of 10 × 12 cm Tegaderm® was the only dressing.

To measure tissue oxygen the reference electrode, incorporated into a three-way tap, was inserted into the hubbed end of the catheter. The tubing was flushed free of air bubbles with saline introduced through the tap. A sheathed platinum-needle electrode (760, Diamond Electrotech, Inc., Ann Arbor, Michigan, USA) was inserted at the opposite end so that its tip was at least 1 cm inside the skin entrance point. A period of 20 min was allowed for equilibration of gases and temperature and for the patient to breathe room air. The electrodes were calibrated at 37°C in a temperature-controlled bath equilibrated to air before and after each set of measurements.

After a baseline value had been established, consisting of two consecutive readings 5 min apart which differed by $\leqslant 2$ mmHg, the patient was given oxygen at 5 litres/min via a face mask (F_{IO_2} 60–70 per cent), and tissue P_{O_2} was recorded at 5 min intervals until constant. If tissue P_{O_2} rose significantly, i.e. by 20 per cent or more, the patient was categorized as well perfused. If tissue P_{O_2} did not rise at least 20 per cent after >20 min of oxygen-breathing, and if it was clinically indicated, blood for arterial gas measurement was drawn while the patient breathed oxygen. The corresponding couplet of tissue P_{O_2} and arterial P_{O_2} was compared with a set of normal values obtained in an earlier study[6] (*Figure 2*). If tissue P_{O_2} was low in relation to the expected or measured arterial P_{O_2}, a supplemental infusion of normal saline 250–500 ml above the ongoing rate was given rapidly. If tissue P_{O_2} rose, the rapid infusion was continued until no further increase was recorded or until tissue P_{O_2} rose into the range of values for normals noted in *Figure 2*. The lower normal limit for air-breathing was taken to be 40 mmHg, and that for oxygen-breathing was $\geqslant 20$ per cent above the air-breathing level. All patients measuring below these levels had arterial gas measurements made or received fluid infusions. Patients whose tissue P_{O_2} was low but commensurate with low arterial P_{O_2} and who responded to oxygen-breathing were classified as adequately perfused.

An increase of 20 per cent in tissue P_{O_2} was chosen to define a significant change because the tissue oxygen measurement is accurate to ±5–10 per cent. Twenty per cent allows minimal chance for erroneous classifications. This definition assumes that arterial P_{O_2} responds to oxygen-breathing. When in individual cases this assumption seemed unwarranted, measurement of arterial P_{O_2} during oxygen-breathing was also clinically indicated and was done. Measurements of tissue P_{O_2} started 2–6 h after operation and were made daily.

It was anticipated that the rate of fluid replacement would affect the tissue P_{O_2}. Therefore, no attempt was made by the investigators to

Table 1 *Operations performed in study patients*

	Total patients (*n*)	Malperfused (*n*)	Indeterminate (*n*)
Major abdominal surgery	30	12	1
Gastric bypass	4	2	0
Biliary	3	1	0
Intestinal resection	13	5	0
Lysis of adhesions	2	1	0
Adrenalectomy (abdominal)	1	0	1
Adrenalectomy (flank)	2	1	0
Recurrent ventral hernia	5	2	0
Peripheral surgery	14	0	1
Mastectomy	11	0	1
Extremity	2	0	0
Thyroidectomy	1	0	0

Table 2 *Clinical data in study patients*

	Packed cell volume (%)					
	Pre-operative	Postoperative	Urine output (ml/h)	Duration of operation (h)	Estimated blood loss (ml)	Age (years)
a *Patients without known pulmonary dysfunction: 40 operations on 38 patients*						
Mean ± s.d.	40·6±4·8	34·7±2·9	92±46	3·1±1·5	330±326	52±16
Range	28·9–51·4	26·7–39·7	30–225	0·75–7·2	5–1000	19–81
b *Patients with history of heavy smoking (> 30 cigarettes/day for > 10 years) and pulmonary dysfunction. Five were operated for recurrent hernia, one had an intra-abdominal operation*						
Mean ± s.d.	40·6±3·7	36·9±1·5	127±42	3·3±1·1	220±153	60±7
Range	33·2–45·4	34·9–39·2	75–200	1·2–4·3	20–500	54–68

Table 3 *Tissue oxygen tensions in patients on the day of operation and up to seven days postoperatively (mean ± s.d., mmHg)*

	Postoperative day							
	0	1	2	3	4	5	6	7
a *Patients without known pulmonary dysfunction: 40 operations on 38 patients*								
Subcutaneous P_{O_2} breathing oxygen	80±27	93±27	70±21	60±16	58±14	59±15	56±18	55±21
Subcutaneous P_{O_2} breathing air	47±7	50±9	47±9	41±8	41±6	41±10	40±10	40±12
b *Patients with history of heavy smoking (> 30 cigarettes/day for > 10 years) and pulmonary dysfunction. Five were operated for recurrent hernia, one had intra-abdominal operation*								
Subcutaneous P_{O_2} breathing oxygen	60±18	60±12*	46±10*	42±12*	43±13*	46±7	43±6	45±9
Subcutaneous P_{O_2} breathing air	38±5*	36±10*	31±5*	29±6*	31±7*	32±4*	34±6	35±6

*Statistically different from group **a** ($P < 0·05$) (Student's double-tailed t test)

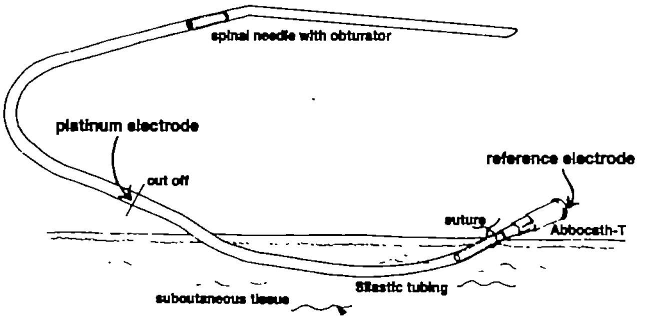

Figure 1 *Silastic catheter for continuous direct tissue oxygen measurements, placed subcutaneously. Reference electrode connected to syringe was flushed with saline before platinum electrode was inserted*

influence the amount of fluid given by the anaesthetists or surgical team who ordered fluid intra-operatively (1–7 litres) and immediately postoperatively (125–200 ml/h). At the time of first oxygen measurement the clinical teams were satisfied with the peripheral perfusion of all patients except one, who had a urine output < 50 ml/h. This patient (no. 6, *Table 4*) had already been given supplemental fluid above the volume originally ordered by the surgical team.

Urine outputs were calculated from the nearest spontaneously voided, timed specimen or by hourly measurements if a urinary catheter was in place.

Results

Figure 3 depicts a typical normal response to oxygen administration. The baseline and peak value of oxygen tend to decrease with the length of time the Silastic catheter has been in place. This probably corresponds to accumulation of inflammatory cells and fibroblasts around the catheter. *Table 2* presents the overall clinical data. *Table 3* presents the mean tissue oxygen values of all patients. The oxygen-breathing values are the means of the peak responses. *Table 3a* summarizes values in all patients who had normal or near normal respiratory function. *Table 3b* shows the mean values for the six patients, all > 50 years old, with histories of heavy smoking

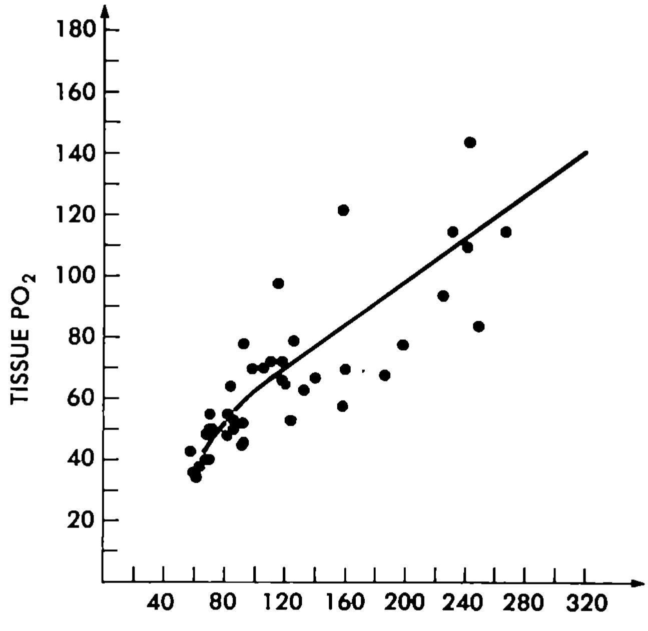

Figure 2 *Relationship between tissue* P_{O_2} *and arterial* P_{O_2} *on day of operation. Reproduced with permission from: Chang N et al. Direct measurement of wound and tissue oxygen tension in postoperative patients.* Ann Surg *1983; 197: 470* © *J. B. Lippincott, Philadelphia, USA*

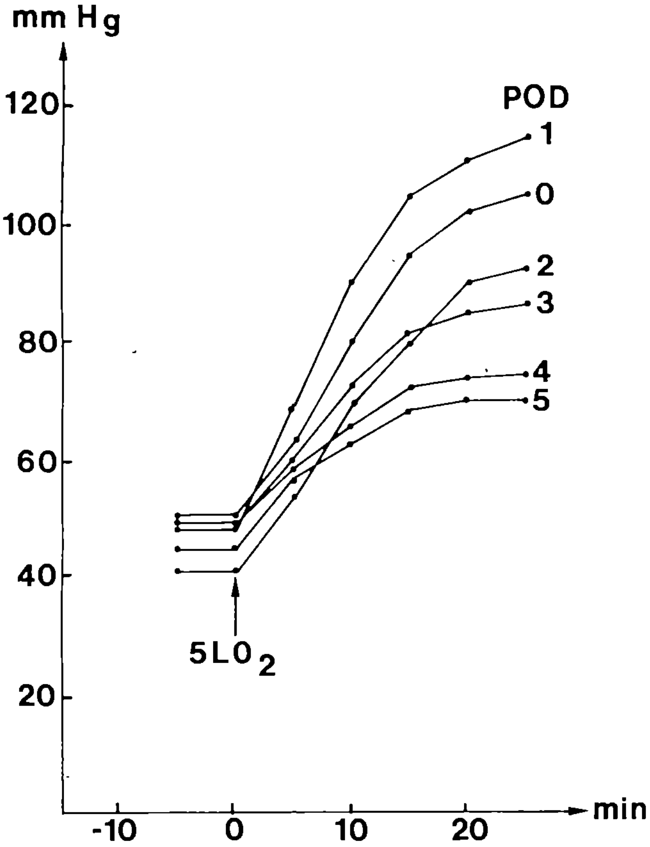

Figure 3 *Baseline tissue* P_{O_2} *levels and rise in tissue oxygen when breathing mixture is supplemented by 5 litres* O_2 *on the indicated postoperative days (POD)*

and/or known pulmonary dysfunction. Five of these had operations for recurrent hernias.

Table 4 summarizes the data from the 12 patients considered malperfused. Only one had a urine output <50 ml/h at any time. All came from the group of 30 patients who had major abdominal operations, including ventral herniorrhaphy. The remaining 18 patients of this group of 30 were normally perfused by all definitions, including urine output >50 ml/h.

Two patients (mastectomy and adrenalectomy via flank) had low tissue oxygen tensions which were unresponsive to oxygen administration and which also failed to rise in response to fluid infusion. They were classified as 'indeterminate' since they did not meet either definition. One recovered uneventfully. The other (adrenalectomy) developed a wound infection. It is possible that this patient was never given enough fluid. No explanation for their unresponsiveness was proved. Arterial P_{O_2} increased significantly in one (adrenalectomy) on breathing oxygen and was not measured in the other. One other patient (no. 11, lysis of adhesions with resection of enterocutaneous fistula) was denied fluid infusion despite low tissue P_{O_2} and remained in a poorly perfused state for 2 days because a normal transcutaneous P_{O_2} measurement was thought to overrule the abnormal subcutaneous value. He came into the normal range when fluid intake was increased on the second postoperative day. His wound became infected.

Tissue hypoxia was associated with heavy smoking and known pulmonary disease in six patients and in them was commensurate with low arterial oxygen tensions. Tissue P_{O_2} responded to oxygen administration in five, and these patients were considered well perfused (*Table 3b*).

Urine output fell <50 ml/h in one patient (no. 6) on two measurements. Each time, the patient was malperfused by oximetric criteria (*Table 4*).

Table 4 *Data on malperfused patients who did not respond to oxygen administration on the first test, but responded after fluid administration*

		Tissue P_{O_2} breathing oxygen						Arterial P_{O_2} breathing oxygen	
Patient no.	Day	Before infusion (mmHg)	After infusion (mmHg)	Difference (mmHg)	Percentage increase	Fluid challenge infusion amount (ml crystalloid)	Urine output (ml/h)	Before infusion (mmHg)	After infusion (mmHg)
1	0	54	65	11	20	1500	140	—	84
2	0	66	100	34	52	650	80	207	227
3	0	44	72	28	63	750	85	—	—
4	0	50	78	28	56	1550	125	164	—
5	0	56	126	70	125	1010	130	—	—
6	0	44	72	28	64	500	30	123	110[a]
	0	47	83	36	77	500	30	—	126
7	0	44	53	9	21	900	120	127	123
8	0	38	48	10	26	1500	180	212	155
9	0	34	42	8	24	1700	50	—	135
10	0	50	70	20	40	1000	110	83	86
11	0	44	48	4	9[b]	500	60	—	—[b]
	0	48±8	71±24[d]	24±18	48±32	1005±451	95±47[e]	153±51	131±46
10	1	57	84	27	47	1000	90	87	101
11	1	45	60	15	33[b]	500 plasma	60	—	—[b]
12	6	30	50	20	67	400 blood	115	106	115[c]
	7	38	54	16	42	1000 plasma	85	130	131
	8	23	32	9	39	500 plasma	95	101	106
	1–8	39±12	56±17[d]	17±7	46±13	680±295	89±20[e]	106±18	113±13

Summary values are mean±s.e.m.

[a] Patient measured immediately postoperatively and 6 h later. The first bolus was insufficient to produce lasting effects. However, by the first postoperative day he was (and remained) well perfused

[b] Clinical problems prevented giving sufficient fluid on the operative day to qualify under present definition. He rose 9 per cent in response to the fluid that could be given. Arterial P_{O_2} measurement was not allowed by the anaesthetist, who was satisfied with a normal transcutaneous P_{O_2}. The next day plasma produced a dramatic effect

[c] Patient was operated upon in shock for intestinal gangrene and eventually died of abdominal sepsis. Permission to measure could not be obtained from the relatives until the sixth postoperative day. At that time, however, blood pressure and urine output were relatively 'normal'

[d] Postinfusion values significantly higher than pre-infusion values ($P < 0{\cdot}001$, paired t test)

[e] Not different from the group without supplemental fluid infusion (91±52 ml)

Discussion

Several score of investigators have demonstrated a relationship between tissue P_{O_2} and perfusion in subcutaneous tissue[6–8], liver[9], kidney[10], brain[11–15], resting muscle[7,16–18], intestinal smooth muscle[19] and pancreas[20]. In theory, the relationship is obvious. The Fick principle states that blood flow, or perfusion, equals oxygen consumption (C) divided by the amount of oxygen actually extracted from blood, i.e. the arteriovenous oxygen content difference (AVD_{O_2})

$$\text{flow} = C/AVD_{O_2}$$

This relationship is particularly easy to demonstrate in subcutaneous tissue, in which oxygen consumption is constant. In this circumstance perfusion and flow are reciprocally related by a constant

$$\text{flow} \times AVD_{O_2} = \text{constant } (C)$$

If perfusion falls, AVD_{O_2} (arterial oxygen content − venous oxygen content) must inevitably increase. Barring changes in packed red cell volume and P_{aO_2}, both of which are easily measurable (and can be assumed constant in this study), AVD_{O_2} can increase only by a fall in the venous P_{O_2} and oxygen content of venous blood. In this circumstance mean tissue P_{O_2} must fall as well, since tissue P_{O_2} in the vicinity of venules is indistinguishable from that of the venules themselves[19]. In simpler terms, tissues extract more oxygen from blood as perfusion falls, and mean tissue P_{O_2} must fall as a consequence.

Mean P_{O_2} in many tissues is 'supported' by the reservoir of haemoglobin-bound oxygen in blood. However, subcutaneous tissue does not normally utilize this oxygen reserve because it uses little oxygen, <1 ml per 100 ml of perfusing blood when perfusion is normal[21]. Its normal mean extracellular P_{O_2} is high, about 60 mmHg (*Figure 2*), well above the range in which haemoglobin releases oxygen readily; i.e., well above the steep portion of the oxygen–haemoglobin dissociation curve[21]. Thus, if perfusion is normal, changes in arterial P_{O_2} from about 60 mmHg upward produce almost equally large changes in mean subcutaneous tissue P_{O_2}[5,9]. However, as perfusion falls and mean tissue P_{O_2} falls into the range of the steep portion of the dissociation curve, elevation of arterial P_{O_2} (breathing oxygen) will raise tissue P_{O_2} by increasingly smaller fractions.

For instance, a tissue which extracts 1 ml oxygen/100 ml blood during normal perfusion will extract 2 ml if perfusion is halved or 3 ml if perfusion falls by 67 per cent. In these circumstances (assuming $P_{aO_2} = 100$ mmHg and packed cell volume = 40 per cent) the P_{O_2} of venous blood draining this tissue (P_{vO_2}) will be 70 or 50 mmHg respectively. If P_{aO_2} is then raised to 300 mmHg, P_{vO_2} will rise to 100 mmHg. But it will rise to only 70 mmHg if perfusion is half normal or 50 mmHg if perfusion is one-third normal. Clearly, as extraction ratio rises, the 1 ml oxygen that can be added to arterial blood by breathing oxygen will change P_{vO_2} and hence tissue P_{O_2} less and less. Lack of response of mean subcutaneous tissue P_{O_2} to breathing oxygen, therefore, itself suggests increased oxygen extraction in subcutaneous tissue and hence poor perfusion there. If infusion of intravenous fluid then increases mean tissue P_{O_2} and its response to oxygen-breathing, the prior presence of malperfusion due to inadequate blood volume is proved.

In this study fluid 'challenge' immediately improved mean subcutaneous tissue P_{O_2} in all but two previously poorly responding patients (classed as 'indeterminate'). The method appears, therefore, to be a sensitive and specific method of detecting depressed perfusion. From the above it is apparent that the method will be more revealing when arterial P_{O_2} is also measured. Tissue hypoxia due to severe arterial hypoxia can be confused with that due to malperfusion if breathing oxygen fails to elevate arterial P_{O_2}.

Oxygen tension of subcutaneous tissues has its own clinical importance. The vast majority of wound infections start in subcutaneous tissue, and vulnerability is a function of oxygenation of leukocytes in the vicinity of the wound[1,2]. In this study four patients had low wound-tissue P_{O_2} for several days, even though vital signs were normal and urine output was >50 ml/h. Three of these patients developed significant wound infections. There were no infections among the well-perfused patients or those who became well perfused early in the postoperative period after fluid replacement. No statistical conclusion can be drawn from this small experience, and further data are being collected.

The rate of collagen accumulation, gain of tensile strength and rate of epithelization in a variety of animal wounds are also proportional to the delivery of oxygen[3,4,22–24]. Poor healing and poor transcutaneous oxygenation in patients have been related by several investigators[25–28]. A transcutaneous P_{O_2} <40 mmHg at amputation sites postoperatively has predicted nonhealing in several studies[25–27]. In particular, Harward has shown an increased correlation when low transcutaneous P_{O_2} is unresponsive to breathing oxygen[28]. Similar relationships based on ^{133}Xe washout curves have been found[29–31]. Both defence against wound infection and rate of wound healing have been clearly related to perfusion in animals by oximetric definitions[1–4,22–24]. Low oxygen tension and low ^{133}Xe clearance have also been correlated with poorly healing intestinal anastomoses[24].

The five patients who had repair of recurrent ventral hernias are relevant to this question. Four of the five seemed to have had anatomically adequate repairs at their initial operations. All four had failed after at least two repairs, and all had low tissue P_{O_2} on the basis of arterial hypoxia while breathing air. Special efforts were made to prevent hypovolaemia in these patients. Even so, one (no. 1, *Table 4*) was 'malperfused' until even more fluid than planned was given on the operative day. Only one of these hernias has recurred again. It was in heavily irradiated tissue in which perfusion is known to be impaired.

Measurement of subcutaneous tissue P_{O_2} may also have greater clinical value, since good perfusion there strongly implies that other tissues are also well perfused. Skin and subcutaneous tissue are felt to be the first sites to be vasoconstricted in response to blood volume deficits and among the last to be restored[7,16,32]. Therefore, if skin is well perfused all other tissues will be well perfused, except, of course, those with impaired regional blood supply. It seems likely, therefore, that these data apply not only to the fate of subcutaneous wounds, but probably to all others except those in tissues whose perfusion is 'protected' during hypovolaemia, namely, heart, brain, liver, lung and kidney. Nevertheless, the degree of clinical significance of subcutaneous P_{O_2} in terms of healing deficits and infection rates remains to be determined. The average perfusion deficit encountered in this study was sufficient to halve subcutaneous P_{O_2} and make it insensitive to the breathing of oxygen. Using the relationships between flow and oxygen tension developed by Piasecki[33], this indicates a perfusion deficit in the region of 50 per cent in the subcutaneous tissues of the poorly perfused patients. This would seem 'significant'.

The impact of temperature on our definition of perfusion has not been fully determined. All subjects had normal core temperatures during measurements. None had notably cool skin. However, subcutaneous temperature was not systematically measured and could have been low in some patients. We have measured it in many postoperative patients, and it has always been 0–3°C less than rectal temperature and less variable than surface temperature. The temperature constant of the electrode system is 2·5 per cent per degree. The observed variability therefore might introduce as much as a 5 per cent error. The fact that fluid challenge improved almost all of the 'non-responders' speaks against a hypothesis that surface hypothermia was a dominant variable, since the fluid challenge is unlikely to have changed subcutaneous temperature in such a short time. Alternatively, warming and fluid challenge might have coincided randomly. This hypothesis is unsupported by the fact that the only two patients who were not challenged with fluid remained unresponsive and five of the patients who were malperfused (i.e., responded to breathing oxygen only after fluid challenge) were >24 h postoperative at the time of measurement (see *Table 4*). Obviously, subcutaneous hypothermia can be either a result or a cause of poor local perfusion. Severe local hypothermia will reduce the utility of subcutaneous P_{O_2} for inferring blood volume or perfusion of other organs, but it would not reduce its significance for inferring infectability or poor wound healing in subcutaneous tissue. Temperature relationships need further study, and the method will be undoubtedly more revealing when subcutaneous temperature is measured simultaneously.

Tissue P_{O_2} in some patients responded to remarkably small volumes of electrolyte solutions. However, the fluid loads were given quickly and measurements were made soon thereafter because we expected fluid challenges to disperse into the extracellular compartment. Nevertheless, *Table 4* shows that patients considered poorly perfused on the operative day and given supplemental electrolyte infusions to the point of good perfusion on that day were usually satisfactorily perfused the next day. The patients who were exceptions clearly had persistent fluid losses (see footnote, *Table 4*). Two poorly perfused patients were not given additional fluid. Both remained poorly perfused.

Clinical measurements of urine output did not correlate with tissue oxygen tension (*Table 4*). In the 30 patients undergoing major abdominal, hernia and flank surgery, 12 were classified as hypoperfused by oximetry. Only one of these was clinically suspected to be hypoperfused because his urine output was <50 ml/h. This left 11 of 30 patients, over one-third of the abdominal surgery patients, suboptimally perfused and undetected by the clinical urine-output standard.

The widely held belief that urine output parallels perfusion of tissues ignores the fact that subcutaneous and connective tissues become vascoconstricted and poorly perfused in response to blood volume deficit and decreased cardiac output long before urine output suffers[34]. In experiments by Nelimarkka *et al.*, renal tissue P_{O_2} fell after 10 per cent blood volume loss, but urine volume decreased only after 20–30 per cent blood volume deficit[10]. Our poorly perfused patients with 'adequate' urine outputs appear to have been in the 10 per cent range of blood volume deficit which may cause peripheral vascoconstriction but does not necessarily decrease urine output.

Acknowledgements

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Early diagnosis of femorodistal graft stenoses

Detection and early correction of stenoses following femorodistal bypass grafting may prevent graft occlusion. We studied 43 grafts (36 saphenous vein and 7 human umbilical vein) prospectively by peroperative angiography and then by clinical assessment, post-exercise Doppler ankle pressures and digital subtraction angiography at 1 week, 3 months, 6 months and 1 year. There were 11 grafts inserted for critical ischaemia, 16 for rest pain and 16 for disabling claudication. Four patients died within the year with five patent grafts and these were excluded from the final results. Eight grafts failed during the first year; four within 1 month and a further four subsequently, with no warning alteration of symptoms, ankle Doppler pressure or digital subtraction angiography. Four additional grafts were jeopardized by symptomatic stenoses. Six grafts developed an asymptomatic stenosis of >50 per cent without a change in exercising ankle Doppler pressure. Three symptomatic stenoses were successfully revised but the fourth occluded on conservative management. Three asymptomatic stenoses have also been successfully revised and three have been treated conservatively. Close surveillance of femorodistal grafts is justified by this study but a deterioration in ankle brachial Doppler index was only useful in the patients with recurrent symptoms and was unable to detect half the stenoses of >50 per cent. The detection of these by intravenous digital subtraction angiography might help to avoid graft failure.

Keywords: Imaging, blood flow, vascular disease

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The patency rate of femoropopliteal grafts is significantly worse than of aorto-iliac reconstruction. For many years these poor results were considered to be due to progression of distal atherosclerosis and a fatalistic approach was adopted, but analysis of the cumulative patency rates in many studies has led to a different conclusion. Some grafts fail within a month (immediate failure) and this can usually be attributed to a technical error. There is then a continuing failure rate over the first year (early failure) and thereafter there is a constant low failure rate each year (late failure). Szylagyi[1] was the first to point out that early failure might be due to stenoses developing within the graft and others have supported this conclusion[2,3]. This has led to more concerted attempts to monitor these patients, since most surgeons agree that infrequent clinical assessment is unlikely to diagnose the failing graft before it thromboses. A graft related stenosis may be treated by a patch angioplasty, a short vein bypass or balloon angioplasty. Revising a functioning vein graft is likely to have better results than either a graft thrombectomy or replacing a failed graft with a prosthetic one[4]. An aggressive approach to the revision of grafts is now taken in many centres[2,4] and every attempt should be made to diagnose these lesions.

Routine use of resting ankle Doppler pressures has been advocated[5] but others have found this to be insufficiently accurate since a drop in the ankle brachial index of up to 0·15 lies within the limitations of the test[6]. The addition of a standard treadmill exercise test reveals some stenoses that would otherwise remain undiagnosed[7].

Until recently the use of standard arteriography in the follow-up of these patients was too invasive to be worthwhile but the advent of intravenous digital subtraction angiography has given us a relatively non-invasive out-patient technique with a low morbidity. The purpose of this study was to compare clinical assessment with ankle Doppler pressure measurement and digital subtraction angiography. First, we compared these three forms of assessment in 28 patients with 32 grafts between 1 month and 6 years after the insertion of a femoropopliteal graft. Secondly, 43 grafts in 41 patients were prospectively studied at fixed intervals through the first postoperative year.

Patients and methods

In a preliminary study 28 patients with 32 grafts were studied between 3 months and 6 years postoperatively. The operation was performed for disabling claudication in 9 patients, rest pain in 12 patients and critical ischaemia in 7 patients. These patients were randomly recalled from a follow-up clinic and consented to have ankle Doppler pressures and digital subtraction angiography performed. They do not represent a consecutive series of patients and only patients with clinically functioning grafts entered the study.

Prospective study

There were 41 patients (31 men and 10 women) with 43 grafts studied prospectively for the first year. The mean age of the group was 63·8 (range 42–78 years); five patients were diabetic but none was polycythaemic or thrombocythaemic. All were smokers pre-operatively but 34 claimed to have stopped smoking since their operation. Carbonmonoxyhaemoglobin levels were not determined.

The graft was inserted for disabling claudication in 16 legs, rest pain in 16 and critical ischaemia in 11 legs. Autogenous long saphenous vein was used on 36 occasions (*In situ* grafts 29, reversed grafts 7) and human umbilical vein was used in 7 legs. Continuous 5/0 or 6/0 Prolene suture was used for the anastomosis.

Each patient had a full pre-operative clinical assessment, Doppler ankle pressure measurements and a conventional arteriogram. Operative arteriograms were performed to ensure that a stenosis was not the result of a technical error but this did not show the proximal anastomosis. This was assessed on intravenous digital subtraction angiography performed 1 week postoperatively. The patients were then reviewed 3 months, 6 months and 1 year after operation. On each occasion they had a clinical assessment, resting and standard exercise ankle Doppler pressures and arteriography. Ankle Doppler pressures were measured at rest and then after 1 min on a horizontal treadmill moving at 3 km/h.

Digital subtraction arteriography was always performed using an

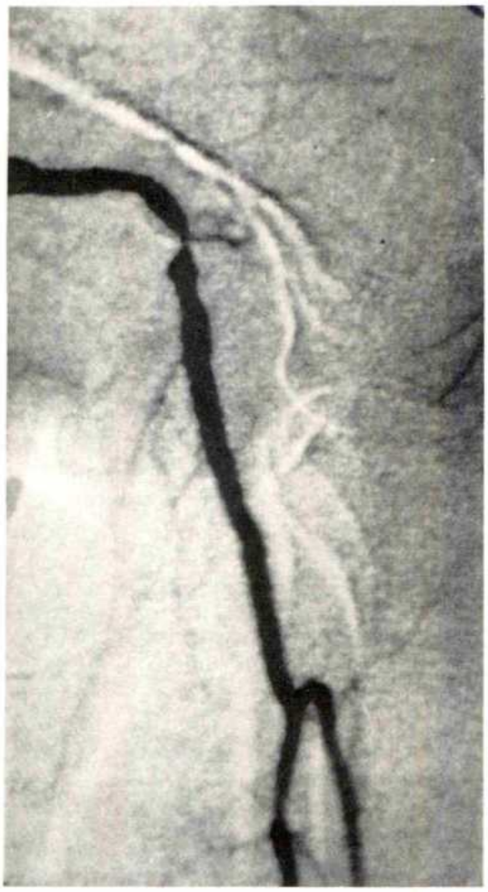

Figure 1 *Lateral view of asymptomatic popliteal artery stenosis with knee flexed. An above knee vein graft had been inserted three years previously*

intravenous injection through a short 16 g cannula in the antecubital fossa or the distal forearm if the brachial vein was unsuitable. Central venous and arterial injections were never used: 50 ml Iopamidol 350 non-ionic contrast medium was layered below 25 ml normal saline and injected[8], using a pump, at the rate of 15 ml s^{-1}.

The angiograms were each reviewed independently by two of us (M.L.T. and J.H.W.) and stenoses >50 per cent recorded.

Results

In the preliminary study of 28 patients with 32 grafts, 6 graft related stenoses were diagnosed: 3 in the iliac artery, 1 in the graft and 2 in the popliteal artery (*Figure 1*). Five of these patients had noticed a deterioration in their symptoms and required arterial reconstruction. The sixth patient had an asymptomatic 6 cm stenosis in the middle third of an *in situ* graft and this graft subsequently failed without further intervention.

Prospective study

There were 41 patients with 43 grafts prospectively studied for 1 year. Four patients died of myocardial infarction between 1 month and 1 year following surgery and all five grafts had remained patent. There were no peroperative deaths: 38 grafts were therefore followed for 1 year and in 26 the symptomatic improvement was maintained, but there was a subsequent deterioration of symptoms in 12 patients. In eight patients the deterioration was due to graft occlusion: four failed within the first month and four failed between 1 month and 1 year. Four out of 36 autogenous vein grafts failed, two within the first month and four out of seven human umbilical grafts failed, two within the first month.

In four of the twelve patients who developed recurrent symptoms the graft remained patent. A mixed arterial/venous ulcer broke down again in one patient, another developed rest pain and the two others developed mild claudication which did not hamper their lifestyle. All four of these patients also had a deterioration in the ankle brachial index >0·15. Digital subtraction angiography revealed a stenosis just above the proximal anastomosis in two (*Figure 2*): in both these patients a local endarterectomy of the common femoral artery was performed. A stenosis in the graft where it kinked at the knee joint developed in one and the fourth symptomatic patient had an occlusion of the popliteal artery. All four of these patients' symptoms were improved by further successful surgery.

A further six grafts developed a stenosis >50 per cent during the year without the patient developing symptoms. In these patients there was no change in ankle brachial index at rest or after a 1 min treadmill exercise test.

Two of these patients were successfully treated by surgical repair and the other four were treated conservatively. Both the surgical repairs were in the common femoral artery just proximal to the graft; one patient had an aortobifemoral graft and the other had a patch angioplasty from the common femoral artery into the hood of the femoropopliteal graft. Four stenoses were treated conservatively and one patient developed a popliteal artery occlusion although the graft remained patent.

Discussion

In this study we hoped to avoid technical errors by operative arteriography and then to detect graft stenoses developing within the first year since 75 per cent of graft occlusions occur during this period[4]. Thereafter, late failures are probably due to progression of atherosclerotic disease[1,9] in vessels and grafts, and while continuing surveillance may help salvage a few grafts, the potential value of frequent angiographic assessment in asymptomatic patients is questionable.

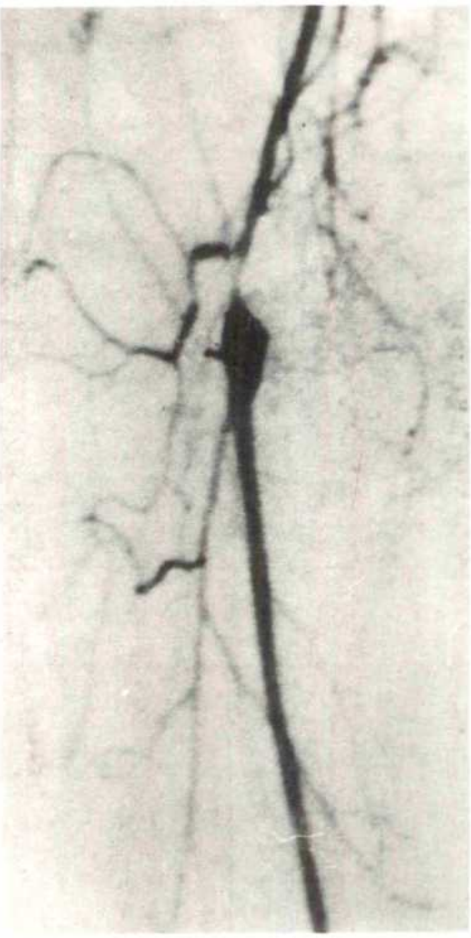

Figure 2 *A symptomatic proximal stenosis developing 6 months postoperatively in endarterectomized common femoral artery. Histology revealed myo-intimal hyperplasia*

Stenoses were equally frequent in the common femoral and popliteal arteries and anastomotic stenoses developed in two grafts. There were no stenoses caused by valve cusps in this study and only two grafts developed an intraluminal stenosis. This appeared to be related to a section of *in situ* vein that became very tortuous when the knee was flexed although it was not distorted in full extension. This study does not confirm previous reports which suggested that the majority of stenoses that developed within the first year are in the graft[1,2]. The stenoses that developed immediately proximal to the *in situ* grafts were shown to be the result of myo-intimal hyperplasia. These lesions developed in the parent vessel adjacent to the anastomosis and may have been caused by damage to the arterial wall by local endarterectomy or minor dissection of the anastomosis. They lay too close to the anastomosis to be due to clamp injury. Histology was not available on the other lesions since they were bypassed.

Digital subtraction angiography is, at present, only available in a few centres in the UK but is likely to become much more widely available within the next few years. We were satisfied with the quality of our images obtained from a peripheral intravenous injection and we do not think that central venous cannulation is necessary in the majority of patients[8]. Since any patient movement destroys the image, the use of a non-ionic contrast material was probably important. This might explain some of the less encouraging reports from the United States where these media have not been available until recently. The femoropopliteal segment is particularly appropriate for this technique since the surrounding tissue is relatively thin and homogeneous. We were satisfied that significant graft stenoses would not be missed using this minimally invasive simple technique. The procedure can be performed without sedation in < 30 min and several out-patient angiograms can be performed in one afternoon. Unfortunately this technique does not yet have the resolution to image accurately anastomoses at the ankle.

This study poses some problems. We have shown that about one in five patients developed a graft related stenosis within the first year but half of these were asymptomatic and did not appear to be haemodynamically significant when assessed by post-exercise ankle Doppler pressures. This raises questions relating to the frequency and method of follow-up. Although we have documented the progression of a popliteal stenosis 4 years after the insertion of a graft the reported failure rates in large series suggest that the benefits of rigorous and frequent follow-up are likely to be most fruitful in the first year and thereafter will have less impact. In our study, those patients who had a fall in ankle Doppler pressure had also noticed a return or deterioration of their symptoms, albeit sometimes mild and untroublesome. Others have found ankle pressures to fall in the asymptomatic patient[5] and in a larger study this group may have emerged. Taylor and Fox[5] overcame the spurious fluctuations in resting ankle pressure index of the grafted leg by relating the pressures to the opposite 'normal' leg but we found that some of the results were difficult to interpret if a deterioration of the index of 0·15 was considered within the limits of error.

Standard exercise testing may unmask stenoses that are missed when the resting pressure alone is measured[7] but even this refinement puts an added strain on time and resources. Furthermore, we were unable to pick up asymptomatic stenoses by this technique.

In order to be aware of all the stenoses, angiography is required (duplex might be an alternative but this also requires expensive equipment). At present we do not know if these additional investigations would prevent graft occlusion and improve limb salvage but it is reasonable to conclude that it is better to repair a functioning vein graft than to replace it with a prosthetic one, and there is evidence to support this premise[4,10]. Although we suspect that a haemodynamically significant stenosis puts the graft in jeopardy and should be revised, we do not know whether a revision can be delayed until symptoms develop or if the graft should be revised immediately. We are currently studying the progression of asymptomatic stenoses and this should allow us to define more accurately the place of angiography during the first postoperative year.

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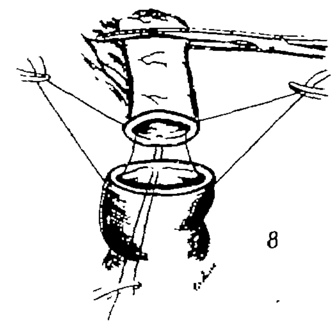
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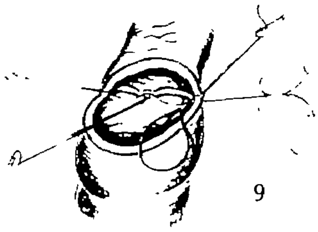
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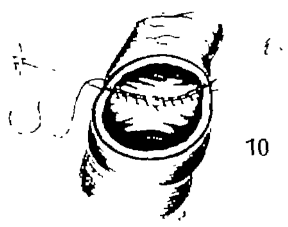
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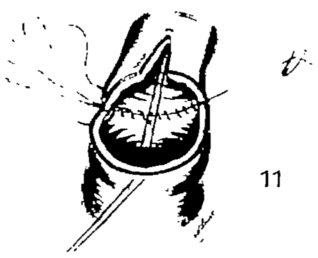
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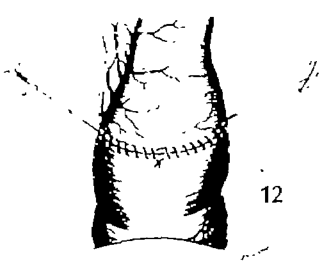
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Use of a gamma camera for measuring limb blood flow in peripheral vascular disease

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A method for measuring limb blood flow during reactive hyperaemia is described. Pneumatic cuffs inflated to 300 mmHg are used to isolate the blood in the limbs from the rest of the circulation. The remaining blood is labelled with technetium. The increase in radioactivity in the limb following release of the cuffs is measured using a gamma camera. The mean rate of flow of blood to the limb (in ml $(100\ ml)^{-1}$ tissue min^{-1}) is derived from the graph of radioactivity versus *time and from the radioactivity in a sample of venous blood. The results of measurements carried out in patients with peripheral vascular disease (30 limbs) and normal controls (24 limbs) are presented. Repeated studies in 10 subjects (20 limbs) showed the method to be highly reproducible at high and low flow rates* ($r = 0{\cdot}99$)*. Case studies illustrating the use of the method as a screening test for peripheral vascular disease and to monitor the effects of treatment are presented.*

Keywords: Blood flow, gamma imaging, peripheral vascular disease

A method for measuring below-knee blood flow with technetium-labelled red cells using a gamma camera has been described previously[1]. The technique was validated with a phantom of a human leg connected to a peristaltic pump and measured flows (obtained with a measuring cylinder and stop watch) were found to differ from calculated flows (obtained from the initial gradient of time activity curves generated from the phantom) by <6 per cent. In the present report the basic technique has been extended to provide information about regional flow within a limb and the method has been adapted for use with arms. In these studies we used technetium-labelled human serum albumin which is much quicker to prepare than labelled red cells.

Case studies are presented illustrating the use of the extended technique on patients with a variety of vascular problems.

Patients and methods

The method has been fully described previously[1]. Briefly, patients are positioned supine with legs and feet over a large field of view gamma camera. The upper limit of the field of view of the camera is marked on the skin with a pen. Pneumatic cuffs 12 cm wide are wrapped around each leg immediately below the knee and are rapidly inflated to 300 mmHg. The purpose of the cuffs is to isolate the blood below the knee from the rest of the circulation and to induce a hyperaemic response. Tracer is administered via an antecubital vein and allowed to equilibrate.

After 2 min 55 s of arterial occlusion, a 10 ml blood sample is taken from the opposite arm. The cuffs are released after 3 min and data is acquired in 1 s frames for 100 s and stored using an on-line minicomputer. The blood sample is then counted on the gamma camera and the background activity is measured. (These data are used to calibrate the inflow curve.) Finally, limb volumes are measured up to the pen marks using water displacement so that flow per unit volume (ml per 100 ml tissue per min) can be calculated.

The stored dynamic data are processed by drawing a region of interest for each limb within the field of view using a light pen and generating time–activity curves. Each curve shows three distinct phases (*Figure 1*): linear phase, when radioactivity in the leg increases at a constant rate and only non-active blood is displaced; exponential phase, which occurs after significant mixing of the tracer within the leg, when blood is leaving the leg through the veins whilst labelled blood of a higher specific activity is arriving through the arteries; equilibrium phase, after complete mixing when activity per unit time flowing in is equal to that flowing out.

The least squares gradient of the linear phase is measured. This represents the rate of arrival of tracer and is proportional to flow. The gradient will also depend on the specific activity of the tracer so we use the 10 ml blood sample taken from the patient to calibrate the gradient to yield flow, F, using equation 1.

$$F = (G/C) \times 60\ \text{ml/min} \qquad (1)$$

where G counts s^{-2} = least squares gradient over the linear phase; C counts $s^{-1}\ ml^{-1}$ = specific activity of the blood sample corrected for background.

The tracer will always record a lower count rate in a limb compared with a 10 ml blood sample. This is because of differences in self-absorption between the two. A correction factor is applied to G to allow for this. The factor for the below-knee portion of the leg was determined using a tissue equivalent leg phantom made from a cast taken from a volunteer.

A 10 ml sample of tracer was counted in a syringe, then this was injected into the phantom and thoroughly mixed. The phantom was

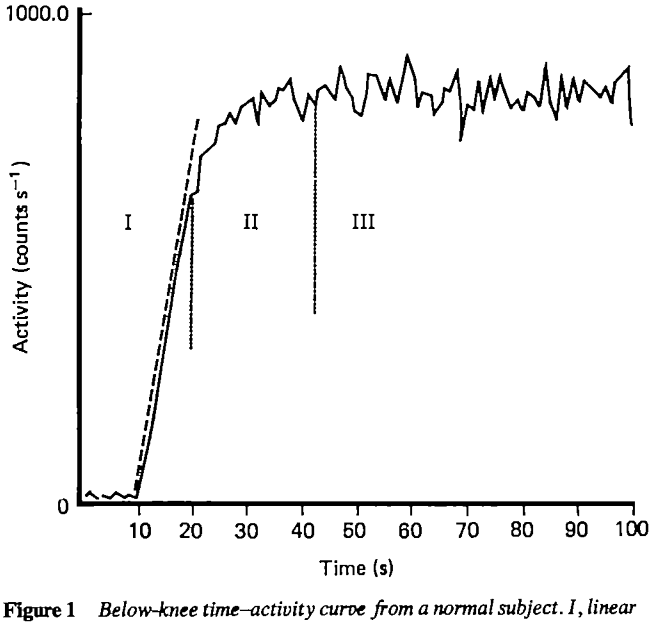

Figure 1 *Below-knee time–activity curve from a normal subject. I, linear phase; II, exponential phase; III, equilibrium phase*

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Table 1 *Self absorption correction factors*

Leg (below knee)	1·3
Calf	1·3
Foot	1·1
Arms (below elbow)	1·1
Forearm	1·1
Hand	1·05

Table 2 In vivo *stability of human albumin*

Subject	Activity at 3 min (1000 count min^{-1})	Activity at 5 min (1000 count min^{-1})	Percentage change
1	15·3	16·9	+10·4
2	13·7	12·6	−8·0
3	21·2	18·6	−12·3
4	44·6	40·0	−9·4
5	62·2	63·4	+1·9
6	17·4	17·8	+2·2
7	15·2	15·1	−0·6
8	14·3	13·7	+4·2
9	17·4	16·5	−5·2
10	28·7	29·1	+1·4
11	24·0	22·0	−8·3
12	27·1	27·2	+0·4
13	34·1	34·4	+0·9
14	24·3	22·7	−6·6

recounted for the same time and the correction factor was determined from the ratio of these counts.

Similar measurements were carried out to determine factors for calf, foot, arm and hand. The results are listed in *Table 1*. The least squares gradient has to be scaled by an appropriate factor before calculating the flow using equation 1. Variation of these factors between patients was assessed by measuring the fractional transmission of radiation from a small radioactive marker through patient limbs and through the limb phantoms. Differences were found to be negligible.

It is in principle possible to extend the basic technique for measuring mean flow of blood to the lower leg (i.e. below the knee) to give regional flow within a leg (yielding for example flow to the foot and calf separately). To calculate the flow to each region separate regions of interest are drawn on the scan with a light pen and time–activity curves generated.

The initial gradients of each curve must again be corrected using a suitable self absorption factor from *Table 1*. One further condition must be satisfied; that is the venous return from distal regions must not augment the apparent arterial inflow into the region above. We can be sure that this is so if the time–activity curve of the distal region remains linear (no loss of activity) during the period over which the gradient of the upper region is calculated.

The tracer used in the previous report[1] was *in vitro* labelled red cells[2]. Although this was found to be quite satisfactory from a technical point of view, the preparation time was considerable. The requirement of a tracer for use in this technique is that there is insignificant clearance from the blood pool between 3 min (before releasing the cuffs) and 5 min (at the end of the dynamic acquisition). Any clearance of tracer during this period will lead to an error since the level of radioactivity in the blood will be changing during the period over which we measure the flow. Technetium-labelled human serum albumin has been used for blood pool scanning[3] and was found to be stable with 85 per cent of administered activity remaining in circulation after 1 h. In our application, early clearance of particles by the liver or of free pertechnetate will not affect the result provided the concentration of tracer is stable between 3 and 5 min after intravenous injection. To test this, patients to be measured were given 400 MBq of tracer (SORIN Biomedica TCK-2) into an antecubital vein and samples were taken from the opposite arm after 3 min and 5 min. The results are shown in *Table 2*.

The mean change was −2·1 per cent with a maximum difference of −12·3 per cent. It is expected that there will be a small reduction in the specific activity because of the unlabelled blood diluting the pool after the release of the cuffs. In patient 1 there appears to be a significant increase in the specific activity with time which was probably due to inadequate mixing at 3 min. This can be overcome by flushing the dose with 20 ml saline and raising the arm to empty the vein. This technique is now routinely adopted.

Results

Figure 2 summarizes the results of measurements on 24 normal control limbs and 30 limbs of patients (similar age range to the controls) with claudication and an arterial occlusion shown on arteriography. For the control group the mean flow per unit volume was 15·6 ± 3·5 ml (100 ml)$^{-1}$ min^{-1} and for the patient group, the mean flow per unit volume was 3·3 ± 2·1 ml (100 ml)$^{-1}$ min^{-1}.

Reproducibility was established by repeating the measurements on 10 subjects (20 limbs) within 2 weeks of the first measurement. The results are summarized in *Figure 3*. The overall correlation coefficient was 0·99 with a mean difference between paired observations of 7·5 per cent. This shows the method to be highly reproducible at high and low flow rates.

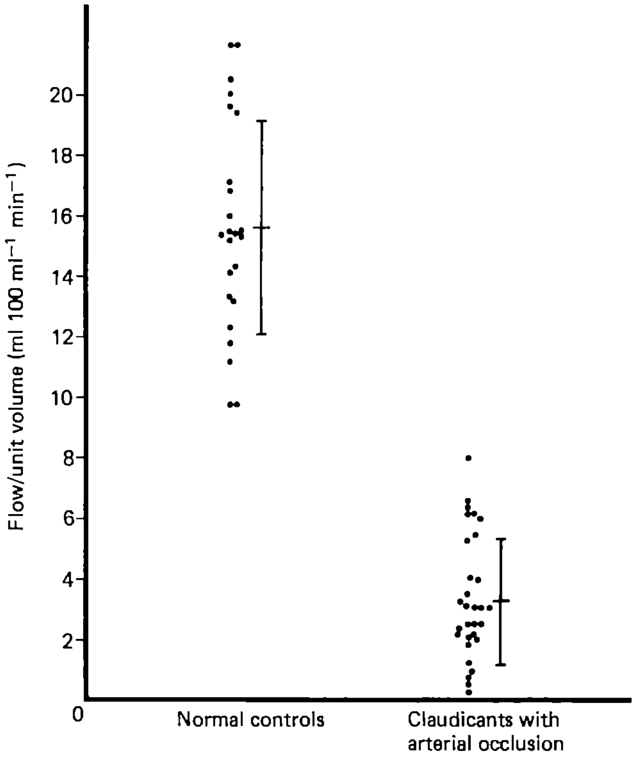

Figure 2 *Blood flow per unit volume in normal controls and patients with peripheral vascular disease*

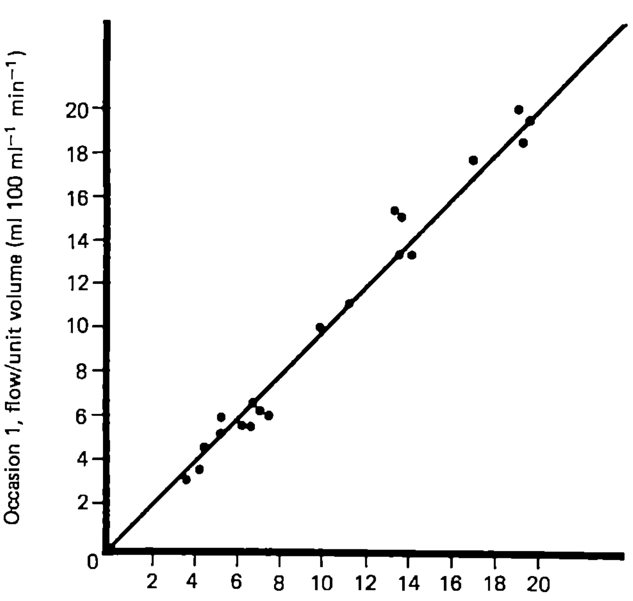

Figure 3 *Reproducibility in 20 limbs*

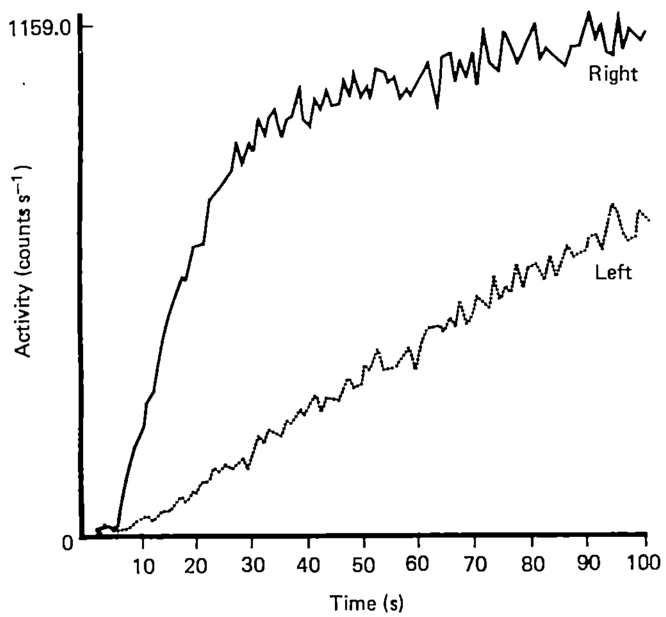

Figure 4 *Time–activity curves from case 1*

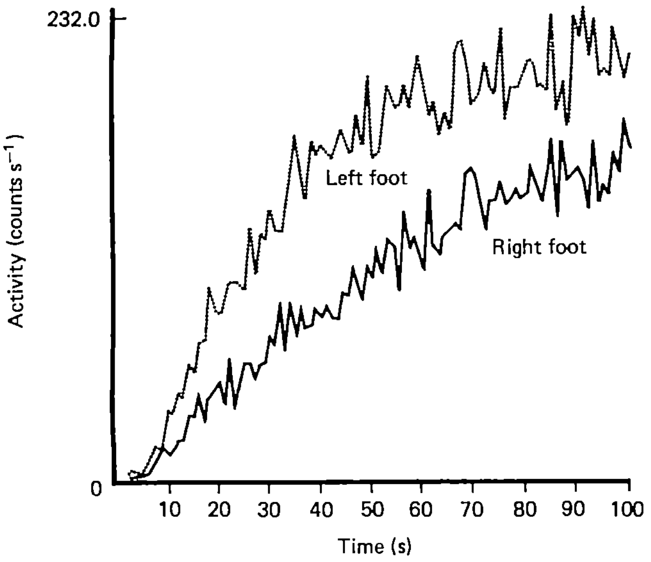

Figure 5 *Time–activity curves from case 2 (feet only)*

The following cases illustrate the use of the technique in a variety of vascular problems.

Case 1

A 73-year old man had severe claudication affecting the left calf and foot. Doppler pressure indices (ankle:brachia) for the right and left legs were 0·6 and 0 respectively. Arteriography showed advanced bilateral disease of iliac and femoral vessels (worse on the left). The time–activity curves are shown in *Figure 4*. The flow to the left limb is so low that the curve is still in the linear phase at the end of the study. However, despite the pulsatile nature of the curve, we can still calculate the gradient of the regression line with confidence. The duration of the linear phase for the right leg is ≈ 25 s which is prolonged (normals are typically 12 s) and again there is no difficulty in calculating the gradient of the regression line. The resulting flows were found to be 107 ml min^{-1} (5·9 ml (100 ml)$^{-1}$ min^{-1}) for the right and 14 ml min^{-1} (0·8 ml (100 ml)$^{-1}$) for the left indicating that the technique can be used with low flow.

Case 2

This case illustrates the use of the technique for measuring regional flow within a limb. A 48-year-old woman had claudication in the right calf and foot after walking 200 m. Doppler pressure indices for right and left legs were 0·6 and 1·0 respectively. Arteriography was substantially normal but failed to visualize the right posterior tibial artery. It was not clear whether this was because the vessel was occluded or masked by the cortex of the tibia. Analysis of time–activity curves showed no obvious differences in flows from the right and left legs until flows in the feet were analysed separately (*Figure 5*). When we translate the gradients into flows the results obtained are shown in *Table 3*.

The deficit in the right foot is significant since none of our normal controls had differences between right and left feet > 10 per cent. The result is consistent with tibial vessel disease.

Case 3

This patient had a 20-year history of a vasospastic disorder diagnosed as Raynaud's phenomenon secondary to rheumatoid arthritis. She suffered classic vasospastic attacks involving all fingers of both hands, the left hand being most severely affected.

Here the method was adapted to measure arm and hand flow. The cuffs were placed above the elbows and inflated. The tracer was injected into a foot vein and flushed with saline The patient was asked to flex the foot for 2 min to assist in mixing. Lead strips were used to demarcate the hands.

A composite view of the scanned dynamic data clearly shows reduced digital flow, particularly to the left hand (marked) (*Figure 6*). Right and left arm flows were found to be 134 and 137 ml min^{-1} respectively and hand flows were 63 and 59 ml min^{-1} respectively.

Case 4

A 64-year-old man presented with symptoms of severe peripheral vascular disease, claudication occurring at 100 yards, the pain affecting both thighs and the right buttock. Clinical examination showed a small aortic aneurysm (confirmed on ultrasound scan) with reduced femoral pulses. Both dorsalis pedis and posterior tibial Doppler pressures were reduced, with pressure indices of 0·5 on both sides. Digital angiography revealed considerable atheroma and a severely stenosed distal aorta and bifurcation. The more distal vessels although diseased were patent. Preoperative isotope limb blood flow studies showed flows of 142 ml min^{-1} (5·7 ml (100 ml)$^{-1}$ min^{-1}) and 155 ml min^{-1} (6·2 ml (100 ml)$^{-1}$ min^{-1}) in the right and left legs respectively. At surgery, a 16 × 8 mm gel-seal graft was used to replace the aneurysmal segment and extended as a Y

Table 3 *Blood flows from case 2*

	Flow (ml min^{-1})	
	Right	Left
Whole limb (below knee)	170	220
Calves only	164	207
Feet only	6	14

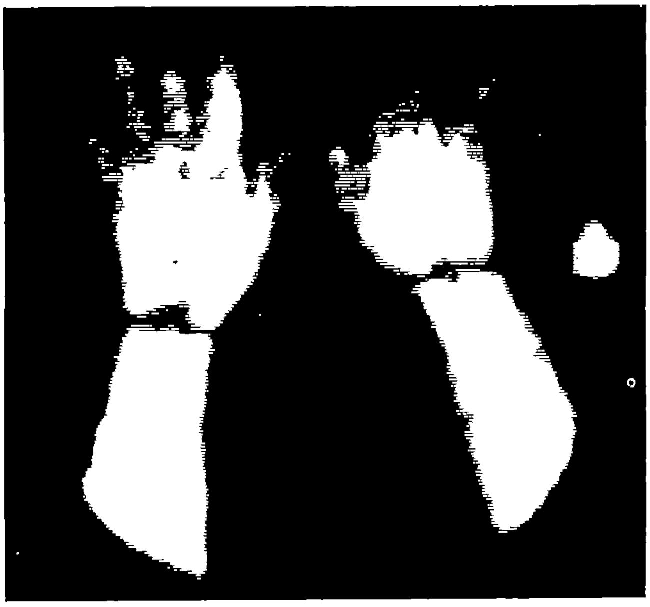

Figure 6 *Summed dynamic image from case 3*

graft to the common femoral arteries. Postoperative recovery was unremarkable and Doppler pressures improved to give a ratio of 0·9 and 1·1 respectively for the right and left legs. He was then free of claudication. A postoperative limb blood flow study revealed flows of $258\,\mathrm{ml\,min}^{-1}$ ($9{\cdot}9\,\mathrm{ml}\ (100\,\mathrm{ml})^{-1}\,\mathrm{min}^{-1}$) for the right leg and $323\,\mathrm{ml\,min}^{-1}$ ($13{\cdot}5\,\mathrm{ml}\ (100\,\mathrm{ml})^{-1}\,\mathrm{min}^{-1}$) for the left.

Discussion

We have selected these cases to indicate the potential of this simple and relatively non-invasive technique. The method is equally applicable to both upper and lower limbs and is acceptable even to those patients with rest pain. The sensitivity of the method is such that it is of value in both high and low flow states. For widespread acceptance any new method of investigation must either offer previously obtained information more easily or offer information that was previously not available. Venous occlusion plethysmography[4–6] is able to measure mass flow but has a poor signal to noise ratio at low flow rates, is subject to a variety of technical errors and artefacts[7] and uses equipment which is not widely available. The isotope method suffers from none of these deficiencies and has proved to be a convenient screening test in those cases where it is unclear whether underlying musculoskeletal disease or arterial occlusive disease is responsible for a patient's symptoms (e.g. case 2) and therefore allows the vascular surgeon to be more selective in those cases he chooses to investigate further with arteriography. The technique may also be used to follow the response of a patient to treatment whether this is by bypass surgery, as in the case we have illustrated, or by balloon angioplasty or medical management. Another field in which the investigation may prove to be of great value is in the selection of amputation sites. The technique may be adapted to allow a regional blood flow measurement to be undertaken and we are currently evaluating such measurements in the choice of amputation levels and the selection of patients for a lateral skew flap technique for a below-knee procedure.

The results of flow measurements in asymptomatic normal volunteers are lower than those obtained by venous occlusion plethysmography. This is to be expected since the major part of hyperaemic flow will go to muscle. The radionuclide method integrates the flow over the whole of the limb below the knee including the foot and ankle which have a relatively small proportion of muscle. Strain gauge plethysmography monitors volume changes over the calf and gravimetric plethysmography includes a large volume of muscle above the knee yielding relatively higher values of perfusion.

It might be expected that the non-active blood returning to the pool would dilute it and change the activity input rate to the leg. This effect is found to be insignificant since the correlation coefficient of the least-squares fit to the linear part of data was found to be $> 0{\cdot}98$ in all cases. The length of the linear phase will depend upon venous capacity and the duration of peak hyperaemic flow. In severe claudicants it was found to be > 100 s, whereas in normal controls it was typically 12 s. With 1 s frames there are sufficient data points to calculate the gradient of the regression line with confidence in both groups.

Flow measurements carried out with a phantom limb and peristaltic pump[1] and our reproducibility measurements in patients with known arterial disease and normal controls indicate that this is an accurate and reproducible method for measuring flow in limbs. The ability to measure simultaneously blood flow to regions within a limb is potentially of great value when planning a treatment strategy.

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Indicators of depressed fibrinolytic activity in pre-operative prediction of deep venous thrombosis

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Euglobulin lysis time (ELT), tissue plasminogen activator (tPA), and the fast-acting inhibitor of tPA, were measured pre-operatively in 128 patients who underwent elective major abdominal surgery. Deep venous thrombosis (DVT) was detected by ^{125}*I-labelled fibrinogen scan in 37 patients (29 per cent) after operation. Pre-operatively, there was diminished euglobulin lysis activity* (332 ± 197 versus 255 ± 156 *min, mean* $\pm$*s.d.;* $P<0{\cdot}025$*), and tissue plasminogen activator activity* ($4{\cdot}2\pm9{\cdot}9$ versus $7{\cdot}7\pm14{\cdot}3$ *milliunits/ml, mean*$\pm$*s.d.;* $P=0{\cdot}094$*) in patients who subsequently developed postoperative DVT compared with those who did not. There was no significant difference between the two groups in the level of inhibition of tissue plasminogen activator* ($160{\cdot}6\pm75{\cdot}4$ *per cent* versus $152{\cdot}5\pm77{\cdot}5$ *per cent, mean* $\pm$*s.d.;* $n=47$*). Stepwise logistic discriminant analysis of the data obtained pre-operatively showed that tissue plasminogen activator, a more specific measure of fibrinolytic activity, was a weaker predictor of DVT than euglobulin lysis time. The results confirm other observations which indicate that lowered fibrinolytic activity is a risk factor for postoperative DVT. In addition, they suggest that this is not due entirely to low levels of activity of tissue plasminogen activator in plasma.*

Keywords: Deep vein thrombosis, fibrinolytic activity

Previous studies in Leeds[1,2] have shown that a predictive index could be derived which accurately identified pre-operatively patients who subsequently developed deep venous thrombosis following elective gynaecological surgery. We have recently shown that similar techniques can be used to predict patients who will develop postoperative DVT after elective major abdominal surgery[3]. In each of these studies, the euglobulin lysis time (ELT), a measure of the level of fibrinolytic activators in blood, has been found to be the single most powerful predictor amongst laboratory measurements of haemostatic function. However, reported results from other studies in general surgical patients have been conflicting. In some cases, a significant reduction, or 'shut down' has been found postoperatively in patients who develop DVT[4,5] but this has not been confirmed by others[6,7]. Attempts to use pre-operative measurement of fibrinolytic activity to predict postoperative DVT have also been unsuccessful[8,9], although the formula developed in Leeds using euglobulin lysis time to predict DVT in gynaecological patients was successfully applied elsewhere[10].

It is likely that at least part of this disparity can be explained by the different techniques used to measure plasma activator activity. These include the fibre plate method[6,7], timed fibrin digestion techniques[5], dilute blood clot lysis time[7], and the technique of Moroz and Gillmore[8]. All of these methods only indirectly measure activator activity in plasma. Recently, specific assays of activator activity have become available which can determine directly the activity of tissue plasminogen activator (tPA) and its fast-acting inhibitor[11,12]. Accordingly, we decided to measure tPA activity and tPA inhibitor in plasma samples which had been obtained during the earlier study into prediction of DVT in general surgical patients[3]. The aim was to determine whether measurement of tissue plasminogen activator or its fast-acting inhibitor could predict the risk of DVT more accurately than measurement of euglobulin lysis time alone.

Patients and methods

The study population consisted of 128 patients aged 40 years or more, who underwent elective major abdominal surgery, and formed the subjects for a larger study into prediction of postoperative DVT[3]. The study was approved by the Leeds Western District Research Ethics Committee. Patients who had clinical or isotopic (^{125}I-labelled fibrinogen scan) evidence of DVT before operation, or those who were taking anti-platelet drugs, oral steroids, or the contraceptive pill, were excluded. Patients were recruited entirely from surgical units in which routine prophylaxis with low-dose heparin was not used and none received specific prophylaxis for the prevention of deep venous thrombosis.

In the morning before operation, a single blood sample was taken, while the patients were still resting in bed after an overnight fast. Blood was obtained through an arm vein using a 19 g needle and without application of a tourniquet. Blood, in the ratio 9:1 by volume, was immediately transferred into pre-cooled (4°C) plastic tubes containing 3·8 per cent trisodium citrate, and processed within 30 min of collection. Citrated blood was centrifuged at 4°C and 2000*g* for 20 min and platelet-poor plasma removed. Euglobulin lysis time ($n=128$) was estimated by the method of Blix[13] on the fresh plasma sample. Assays for activity of tissue plasminogen activator ($n=109$) and inhibitor ($n=47$) were carried out on plasma which was frozen and stored at −70°C to preserve activity of plasminogen activator and its inhibitor which is known to be labile. Storage of samples at −70°C does not significantly alter fibrinolytic activity in plasma[14]. The assays for tissue plasminogen activator and inhibitor became available only after the study had been initially designed and were not used in the original predictive formula. Activity of tissue plasminogen activator was measured in euglobulin fractions of plasma by a chromogenic substrate method[11]. Fast-acting inhibitor of tissue plasminogen activator was measured by a modification of the spectrophotometric activator assay[12,15]. In a total volume of 250 μl, containing 0·1 mol/l tris HCl pH 7·5, 0·1 per cent (v/v) Tween 80, 0·3 mmol/l H-D-Val-Leu-Lys-pNA (S-2551), 0·13 mol/l plasminogen, and 25 μl plasma, varying amounts of tPA were added (0–4 units/ml plasma), and the resulting activity was measured. The amount of purified melanoma tissue plasminogen activator (specific activity 50 000 units/mg) which just neutralized the inhibition was taken as a measure of the inhibitor level. Inhibition was expressed as a percentage, relative to inhibition of pooled normal plasma, 100 per cent inhibition representing approximately 0·7 units/ml of inhibitor activity. Recently, we established that our unit measurement corresponds with 6 international units of the standard for tissue plasminogen activator[16].

Deep venous thrombosis was diagnosed by the ^{125}I-labelled fibrinogen leg scan technique, using the criteria of Kakkar[17]. Patients were scanned on the day before, and on the first, third and sixth days after operation, or daily if the scan became positive. Patients who developed positive leg scans with high counts extending into the thigh also underwent bilateral ascending venography.

Statistical analysis

To test for significant differences between the two groups of patients, a non-parametric test, the Mann–Whitney *U* test, was used. Stepwise logistic discriminant analysis was carried out to determine the power of the variables as pre-operative predictors of DVT, and to construct a predictive index as described in detail elsewhere[3]. Results are expressed as mean and s.d. unless otherwise indicated.

Results

One hundred and twenty-eight patients were studied. The operations performed were: 50 gallbladder (39 per cent), 37 colorectal (29 per cent), 20 gastric (16 per cent), 12 vascular (9 per cent), and 9 miscellaneous (7 per cent). Thirty-seven (29 per cent) of the patients developed postoperative DVT. Two factors were found to be strongly predictive of postoperative DVT: age and euglobulin lysis time (ELT). This enabled an index to be calculated, $I = -11{\cdot}5 + 0{\cdot}133$ age (years) $+ 0{\cdot}006$ ELT (min). Tested prospectively, this was found to have a sensitivity of 93 per cent and a specificity of 83 per cent in prediction of postoperative DVT[3]. Euglobulin lysis time was significantly longer (332 ± 197 min) in patients who developed DVT than in those who did not (255 ± 156 min; $P < 0{\cdot}025$). Measurement of the inhibitor of tissue plasminogen activator on a sub-set of patients ($n = 47$) did not suggest that it was likely to be useful in detecting risk of DVT (*Figure 1*). Accordingly, assays of inhibitor of tissue plasminogen activator were not carried out on further stored samples, and values of the inhibitor were not tested in the predictive formula for their ability to predict DVT. Activity of tissue plasminogen activator in plasma (*Figure 2*) was lower in patients with postoperative DVT ($4{\cdot}2 \pm 9{\cdot}9$ milliunits/ml), than in those without ($7{\cdot}7 \pm 14{\cdot}3$ milliunits/ml), though the difference between the groups was not significant ($P = 0{\cdot}094$). There was a highly significant correlation between activity of tissue plasminogen activator and activator levels measured indirectly by euglobulin lysis time and expressed as units ($r = 0{\cdot}77$, $P < 0{\cdot}001$; *Figure 3*). However, when measurement of plasma tissue plasminogen activator was substituted for euglobulin lysis time (ELT) in the logistic discriminant analysis, there was no improvement in the predictive power of the index. Similarly, substitution of euglobulin lysis activity as units ($10^6/\text{ELT}^2$) produced a weaker predictive index than euglobulin lysis time expressed in minutes.

Cigarette smokers have a lower risk than non-smokers of

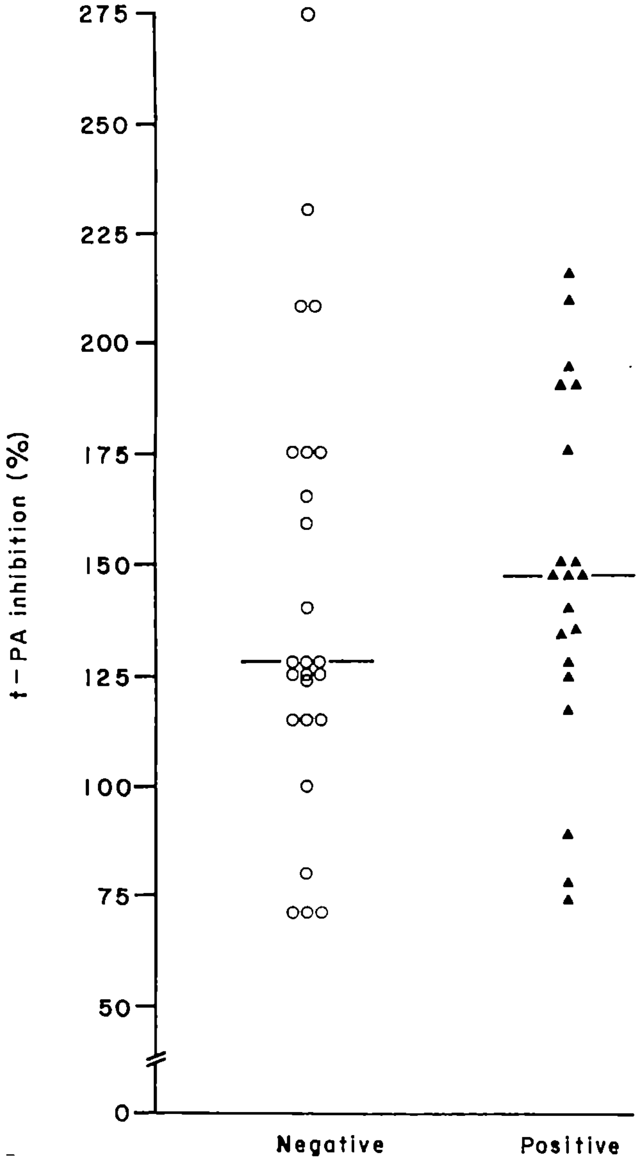

Figure 1 *Pre-operative measurements of tissue plasminogen activator inhibitor activity in the blood of patients with postoperative deep vein thrombosis and those without* (n = *47*)

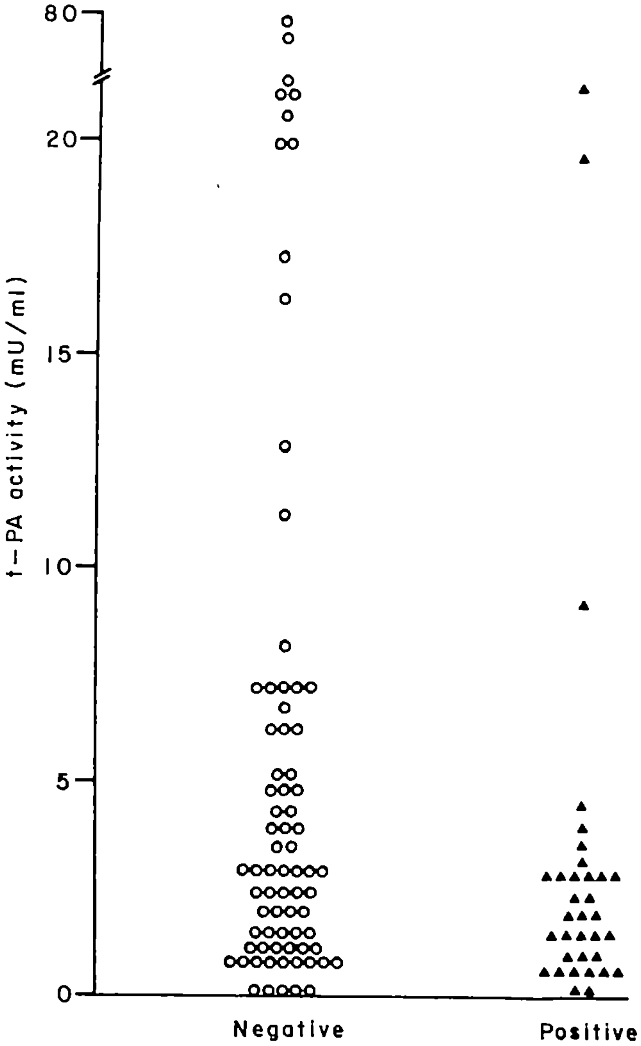

Figure 2 *Pre-operative measurements of tissue plasminogen activator activity in the blood of patients with postoperative deep vein thrombosis and those without* (n = *109*)

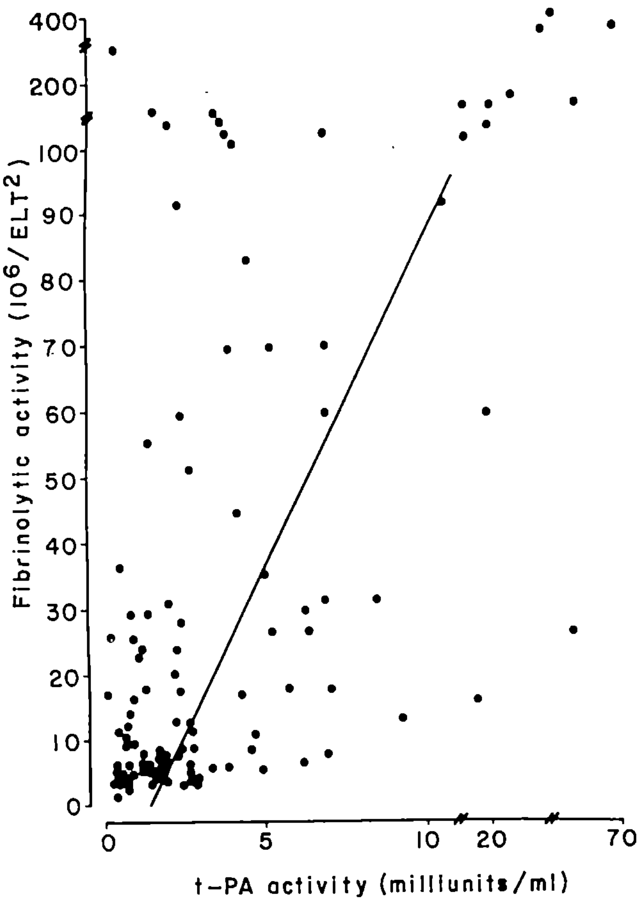

Figure 3 *Relationship between pre-operative measurements of plasma tissue plasminogen activator and euglobulin lysis activity expressed in units* (*10^6/ELT^2*)

developing postoperative DVT. We examined the values for tissue plasminogen activator in relation to smoking habit (*Figure 4*) but there was no significant difference in plasma concentrations between smokers and non-smokers (10·7 ± 18·7 *versus* 4·3 ± 7·9 milliunits/ml; $P=0{\cdot}16$).

Discussion

Activators of the fibrinolytic system found in the circulation are thought to be derived both from extrinsic and intrinsic sources. Activator of the extrinsic system of fibrinolysis, tissue-type plasminogen activator (tPA), has been shown to originate mainly from vascular endothelial cells[18,19]. The concentration of tissue plasminogen activator in plasma as determined immunochemically is significantly lower than would correspond to its activity as measured indirectly by euglobulin and clot lysis methods[12,20]. This apparent discrepancy can be explained by the recent finding that a portion of tissue plasminogen activator in blood circulates in complexes with inhibitors and is inactive[21]. The availability of tissue plasminogen activator is dependent not only on its release from the vascular endothelium, but also upon its neutralization by circulating inhibitors. A fast acting inhibitor of tissue plasminogen activator in the blood has been demonstrated by several groups[12,22], and only recently have specific assays for activity of this inhibitor been described[12]. It has been shown that patients with low plasminogen activator activity in their blood are at increased risk of DVT postoperatively[4,5], and of recurrent spontaneous DVT[23]. In the construction of a predictive index to identify patients pre-operatively who are at increased risk of postoperative DVT, we have consistently found low levels of fibrinolytic activator, measured as euglobulin lysis time, to be an important predictor[1,3]. We carried out the present study to determine whether the observed reduction in fibrinolytic activator activity was due to lower levels of activity of tissue plasminogen activator, or to increased levels of its inhibitor.

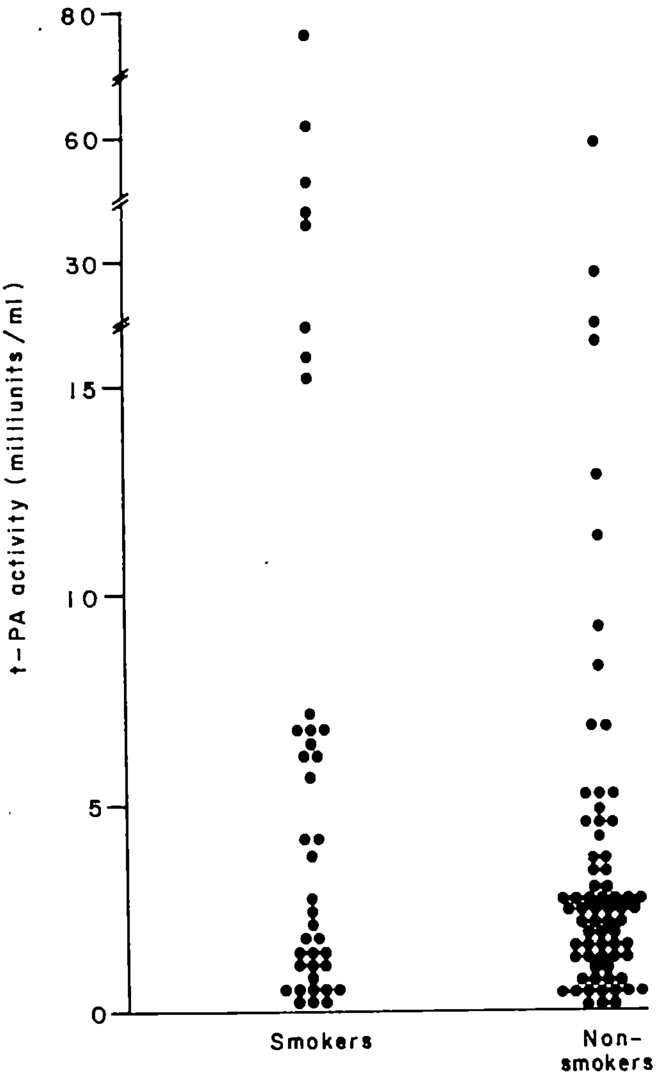

Figure 4 *Pre-operative measurements of tissue plasminogen activator activity in the blood of smokers compared with non-smokers*

Pre-operative assays of tPA inhibitor did not reveal any major differences between the groups (*Figure 1*). The finding is consistent with those previously reported[24]. Although the pre-operative level of tissue plasminogen activator activity was lower in patients with postoperative DVT than in those without, the difference was not statistically significant ($P=0{\cdot}094$). Measurement of tissue plasminogen activator also proved to be a weaker predictor of thrombotic risk than measurement of euglobulin lysis time when substituted in the predictive index. This finding was unexpected, and suggests that activators of plasminogen other than tissue-type plasminogen activator might be relevant to the protective effect of the fibrinolytic system against the development of venous thrombosis. This possibility is supported by the deviations from ideal correlation between measurement of tissue plasminogen activator and euglobulin lysis time (*Figure 3*), which also suggests that activators other than tissue plasminogen activator probably contribute to euglobulin lysis activity. Such activators may be derived from the intrinsic fibrinolytic system[25].

A considerable overlap in the pre-operative clinical and laboratory measurements was observed between patients who did and those who did not develop DVT. No single factor emerged which could accurately discriminate between the two groups of patients. This is consistent with the probable multifactorial aetiology of DVT. While diminished fibrinolytic activity in blood is an important contributory cause of venous thrombosis, it is not in itself sufficient, and in those patients with fibrinolytic activity well within the normal range who suffered

DVT, presumably of less significance than other aetiological factors such as old age. We have sought to overcome the weak predictive power of single measurements by using a combination of risk factors identified by the technique of logistic discriminant analysis to predict the presence or absence of DVT. This approach has proved to be accurate in the pre-operative identification of patients at high risk of DVT[3], though such mathematical models which use a probability risk score to predict outcome will inevitably misallocate a few patients.

Cigarette smoking has been reported to confer a degree of protection against DVT[26,27], a finding which was confirmed in the larger study[3]. It has been reported that cigarette smoking enhances fibrinolysis by increasing activity of tissue plasminogen activator[28]. In the present study, mean tissue plasminogen activator activity was twice as high in the blood of smokers compared with non-smokers, though the difference was not statistically significant ($P=0{\cdot}16$). Similarly, there was no significant difference in euglobulin lysis activity between the two groups. Accordingly it seems unlikely that the protective effect of fibrinolytic activators in the blood is linked to the effect of smoking.

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Acute superior mesenteric ischaemia

A review of case records and post-mortem reports from Glasgow Royal Infirmary over the past 12 years identified 102 patients with acute superior mesenteric ischaemia, 53 (52 per cent) of whom were first diagnosed at post mortem. Overall mortality was 92 per cent and mortality in the 49 patients diagnosed in life was 84 per cent. Fourteen patients (14 per cent) underwent exploratory laparotomy only with no survivors, 26 (25 per cent) had bowel resection alone with 7 surviving, and 9 (9 per cent) had a revascularization procedure, 5 requiring additional bowel resection, with only one surviving. Survivors were usually younger, had a shorter history and less extensive bowel infarction. Improvements in intensive care and nutritional support with the greater use of revascularization procedures in the past 6 years have barely influenced mortality. Delays in diagnosis and treatment contribute to the poor results. Earlier diagnosis might be aided by measuring serum inorganic phosphate and, coupled with the more widespread use of emergency angiography and revascularization procedures, holds out the best hope for future improvement.

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Almost 30 years have elapsed since the first successful embolectomy for superior mesenteric artery embolism[1] and 49 successful cases had been reported by the end of 1974[2]. Despite some enthusiasm for revascularization, resection remains the mainstay of treatment for mesenteric infarction and the overall survival rate appears to have changed little.

We have reviewed our experience of acute superior mesenteric ischaemia to document the incidence, aetiology and mortality of the condition and to attempt to define any factors which may lead to an improvement in outcome.

Patients and methods

A review of case records and post-mortem reports from Glasgow Royal Infirmary between January 1973 and August 1984 identified 102 patients with acute superior mesenteric ischaemia. Important exclusions were patients with strangulation due to hernia, adhesions or volvulus, patients with infarction associated with chronic arterial occlusion or venous thrombosis and patients with ischaemic colitis which tends to be viewed as a separate entity[3]. Forty-nine patients (48 per cent) were diagnosed at laparotomy and the remainder at post mortem; 72 patients (71 per cent) overall having had a post mortem performed. At the time of this study the catchment population averaged around 200 000.

Mesenteric ischaemia was attributed to embolism on the demonstration of an embolus at post mortem or laparotomy, and in three other patients with mesenteric infarction at laparotomy, because of embolism elsewhere in two and previous embolism in one. Arterial thrombosis was defined as the presence of occluding thrombus diagnosed at laparotomy or post mortem without evidence of embolism elsewhere. Non-occlusive mesenteric ischaemia was diagnosed when the mesenteric vessels were patent with no small vessel disease evident on histology. Patients in whom the underlying cause of ischaemia was not or could not be determined at laparotomy were analysed as an unknown aetiology group. They had none of the characteristic features of mesenteric venous thrombosis and were considered to have an arterial aetiology. Two other patients had ischaemia due to a dissecting aortic aneurysm and syphilitic aortitis with aneurysm formation respectively.

Statistical analysis was by χ^2 test.

Results

Of the 102 patients reviewed, 55 (54 per cent) presented in the latter half of the study. The number of patients diagnosed in life increased in the last 6 years (29 *versus* 20), whereas the numbers diagnosed at post mortem were little changed (26 *versus* 27).

The patients were analysed in five groups according to aetiology (*Table 1*) and the age and sex breakdown of the groups with the mortality rate of each is shown in *Table 2*. Eight patients survived the initial episode giving an overall mortality rate of 92 per cent and a mortality rate for the 49 patients diagnosed in life of 84 per cent. There was no significant improvement in the survival rate over the 12 years of the study; three patients (6 per cent) survived in the first 6 years compared with 5 (9 per cent) in the second 6 years.

Pre-existing vascular disease, predominantly ischaemic heart disease and peripheral vascular disease, was a common feature (*Table 3*). Eight patients had a history of embolism, six of whom presented with infarction due to mesenteric embolism. Twenty-two patients presented with concomitant vascular disease, usually a cerebrovascular accident or acute limb ischaemia, but in only half was embolism the common cause of both pathologies. The extent of the bowel infarction varied, 67 per cent of patients with arterial thrombosis having extensive infarction involving small bowel and colon. Of the 49 patients diagnosed in life, 53 per cent were admitted within 24 h of the

Table 1 *Patient breakdown into aetiological groups*

	Totals	Post mortem evidence	Operative evidence	Other evidence
Embolism	34 (33)	28 (82)	3 (9)	*3 (9)
Arterial thrombosis	27 (26)	19 (70)	8 (30)	—
Non-occlusive ischaemia	24 (24)	23 (96)	1 (4)	—
Unknown aetiology	15 (15)	0 (0)	15 (100)	—
Miscellaneous	2 (2)	2 (100)	—	—
Totals	102	72 (71)	27 (26)	3 (3)

Values in parentheses are percentages
* Embolism elsewhere (2), previous embolism (1)

Table 2 *Age, sex and mortality of aetiological groups*

Aetiology	Number	Male:female	Mean age (years)	Alive	Mortality (%)
Embolism	34	14:20	63 (38–87)	2	94
Arterial thrombosis	27	13:14	66 (42–87)	2	93
Non-occlusive ischaemia	24	12:12	69 (48–81)	0	100
Unknown aetiology	15	5:10	69 (55–89)	4	73
Miscellaneous	2	2:0	60, 71	0	100
Totals	102	46:56	66	8	92

Table 3 *Analysis of major aetiological groups*

Factors	All	Embolism	Arterial thrombosis	Non-occlusive ischaemia	Unknown aetiology
Total group	102	34	27	24	15
Previous vascular disease (%)	62	53	63	75	67
Previous embolism (%)	8	18	4	4	0
Concomitant vascular disease (%)	22	32	15	29	0
Small bowel and colon infarction (%)	44	32	67	37·5	47
Patients diagnosed in life	49	18	12	3	15
Admission with 24 h (%)	53	89	42	34	27
Surgery on day of admission	47	50	50	67	40
Patients diagnosed at post mortem	53	16	15	21	0
Diagnosis unsuspected before post mortem (%)	60	69	53	62	0

onset of symptoms and 47 per cent had laparotomy on the day of admission. Those presenting later tended to have positive abdominal findings and consequently had laparotomy performed sooner after hospitalization. The diagnosis was unsuspected in life in 60 per cent of the 53 patients diagnosed at post mortem; in the remainder the diagnosis was suspected, but the patients' condition precluded surgical treatment.

Investigations

Serum amylase (normal range 70–300 units/l) was checked in 52 patients (51 per cent) on admission and was elevated in 27 (52 per cent), reaching the diagnostic range of acute pancreatitis (> 1200 units/l) in 3 (6 per cent of the original 52). White cell counts were checked in 37 patients (36 per cent) and were elevated in 31 (84 per cent), 20 of whom had counts above 15×10^9/l. Lactate dehydrogenase was checked in seven patients and was found to be elevated in five, three of whom had had recent myocardial infarctions. Phosphate was determined in only three patients and was elevated in two.

Pre-operative angiography was performed in only one patient. He was admitted 3 weeks after coronary artery bypass grafting with a 3 h history of epigastric pain with coldness and numbness of both hands. Abdominal examination was negative but arm pulses were absent bilaterally. Diagnostic possibilities included embolism or an aortic dissection. Angiography confirmed emboli in the superior mesenteric and both subclavian arteries. At laparotomy the bowel, although ischaemic, was not infarcted and embolectomy was successfully performed with improvement in the bowel colour. Bowel viability was confirmed at laparotomy 2 days later.

Surgery

Forty-nine patients (48 per cent) underwent laparotomy and were thus diagnosed in life. Fourteen patients (14 per cent) had exploratory laparotomy only, usually because of massive bowel infarction too extensive for resection, and all died. Twenty-six patients (25 per cent) underwent resection alone, of whom seven (27 per cent) survived. Survivors usually had a shorter history, were operated on sooner and required less extensive bowel resection.

Nine of the patients (9 per cent) underwent direct arterial surgery consisting of superior mesenteric embolectomy in seven, aorto-mesenteric graft in one and negative arterial exploration in the other, five requiring additional bowel resection. Only one patient survived, recurrent infarction being the major problem in the remainder. Embolectomy has been increasingly attempted. Since 1979, six out of eight patients with an operative diagnosis of embolism have undergone embolectomy compared with only one out of 10 patients in the preceding 6 years.

Four patients had planned second-look laparotomies within the first 48 hours. Viable bowel was found in two and both survived. Two patients had more infarcted bowel and both succumbed despite one undergoing a second bypass grafting and further bowel resection. Five additional patients had further surgery for clinical deterioration between the third and eighteenth days following their first operation, all dying of recurrent infarction or anastomotic breakdown with intra-abdominal sepsis.

Embolism

Embolism was the commonest cause of infarction, accounting for 33 per cent of cases. Atrial fibrillation was present in 22 patients (65 per cent). Four patients embolized while on oral anticoagulants, two others having discontinued therapy recently. The source of embolus was cardiac in 24 patients (71 per cent), including seven with mural thrombus following myocardial infarction and five with rheumatic heart disease. Five patients embolized thrombus from atheromatous plaques in the proximal aorta, and in five patients no source of embolus was identified. Patients with rheumatic heart disease were younger than those with myocardial infarction or atheroma (mean age 54 years *versus* 65 years and 68 years respectively).

Arterial thrombosis

Patients with arterial thrombosis tended to have more extensive infarction and a more insidious onset of symptoms than those with embolism. Six of the 27 patients (22 per cent) had a history of abdominal pain and weight loss suggestive of intestinal angina. Four had been extensively investigated, one having undergone laparotomy and two others developing mesenteric infarction while awaiting angiography.

Non-occlusive ischaemia

Non-occlusive mesenteric ischaemia was most commonly diagnosed at post mortem, only three patients having had laparotomy. Precipitating events included myocardial infarction in seven, cardiac failure in six, recent major surgery in two (oesophagogastrectomy and extensive orofacial surgery for carcinoma) and surgery for severe haemorrhage in two (bleeding duodenal ulcer and severe epistaxis), hypotension commonly being an associated factor.

Discussion

The greater number of patients with acute superior mesenteric ischaemia presenting in the past 6 years, despite a 23 per cent reduction in the catchment population over this period, suggests an increasing incidence and perhaps reflects our progressively ageing population. Mesenteric embolism in a young patient with rheumatic heart disease is now a rarity and our patients are characteristically elderly 'arteriopaths'. The mortality rate in this series is unchanged from that reported 20 years ago[4,5] and, despite the increasing number of revascularization procedures performed in the past 6 years, most survivors (seven out of eight) underwent resection alone. If the mortality rate is to be improved attention needs to be directed towards earlier diagnosis and revascularization.

Embolism was typically associated with an acute onset of symptoms and, although the majority (89 per cent) of those diagnosed in life were admitted within 24 h of the onset of symptoms, only half were operated on that day. Only two of the patients having embolectomy were operated on within 24 h of the onset of symptoms, one surviving and the other requiring additional bowel resection. Of the five others treated after 24 hours, embolectomy probably resulted in smaller areas of bowel resection in three patients. Extensive resections were still necessary and all succumbed within a few days of surgery. Several small series have reported promising results from embolectomy[2,6] and the importance of prompt diagnosis and treatment to the success of surgery has been emphasized[2]. The delay to surgery appears to have been a major factor in our lack of success. In a larger series of patients, despite successful embolectomy with restoration of peripheral mesenteric pulsation in 29 of 30 patients, only 8 (26 per cent) survived[7]. Mesenteric vasoconstriction persisting after embolectomy is considered by some to explain the poor results of seemingly successful surgery and with the use of intra-arterial papaverine pre- and postoperatively, survival was achieved in 55 per cent of 20 patients[8].

Surgery for acute arterial thrombosis by endarterectomy or aortomesenteric shunt is more problematic and rarely successful due to the high re-thrombosis rate[7] and the often extensive bowel infarction. In our experience the insidious onset of symptoms usually delayed presentation and the opportunity for revascularization was missed.

In a comparable study from the USA, non-occlusive mesenteric ischaemia was reported to account for 50 per cent of cases[5]. While the incidence was lower in this series, perhaps because of our low hospital post-mortem rate (currently around 20 per cent), we also found 100 per cent mortality. A breakthrough in the treatment of this condition has been reported from a study[6] in which defined 'at risk' patients with persistent abdominal pain were subjected to emergency angiography. This approach permitted the early diagnosis of mesenteric ischaemia and the opportunity of selectively perfusing the mesenteric circulation with vasodilators via the angiography catheter. Drawbacks include the number of negative examinations (ranging from 30 per cent[6] to 52 per cent[9]) performed in these ill, often high risk patients and the possible erroneous diagnosis of mesenteric ischaemia in patients with a previous silent visceral artery occlusion[3]. Nevertheless, this approach to the investigation and management of patients with mesenteric ischaemia appears promising and may well be the initial treatment of choice in non-occlusive mesenteric ischaemia where the traditional surgical approach is of limited value. Despite our infrequent application of the technique to date, we would advocate greater use of emergency angiography when the diagnosis of acute mesenteric ischaemia is considered, unless the consequent delay might prejudice the success of any subsequent revascularization.

'Second-look laparotomy' provided reassurance in two patients in whom there was doubt about bowel viability at the end of the first operation, but two others with further infarction died. In a larger series the decision to re-explore was usually correct[7] and we would support a policy of selective 'second-look laparotomy', based partly on the condition of the remaining bowel at the end of the first procedure.

It is disappointing that despite the greater use of revascularization procedures with improvements in nutritional support and intensive care, we have made little impact on the mortality rate of this condition in the past 6 years. Our experience is, we suspect, typical of other UK centres. Earlier diagnosis of the condition requires first and foremost a high index of clinical suspicion. The presence of hyperphosphataemia is strongly suggestive of mesenteric ischaemia[10], particularly when accompanied by leucocytosis[11] and metabolic acidosis[12]. Emergency angiography will confirm the diagnosis and the exact cause thereby permitting a rational plan of treatment which might include vasodilator therapy with papaverine and/or direct arterial surgery. Only by adopting this more aggressive approach to the diagnosis and treatment of mesenteric ischaemia can we hope to influence the continuing high mortality.

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Prevention of gastric mucosal lesions following aortic cross-clamping

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Stress ulceration is frequently encountered after cardiovascular surgery. In this study of 32 male baboons, severe gastric ischaemia was used to produce gastric stress lesions. The occurrence of these lesions was reduced by allopurinol ($P=0{\cdot}03$) *and completely prevented by the combination of allopurinol with superoxide dismutase* ($P=0{\cdot}004$). *A shorter ischaemic period also reduced the number of lesions* ($P=0{\cdot}02$). *Concurrent with the stress lesion formation, there was a fall in mucosal glutathione and oxidized glutathione levels* ($P<0{\cdot}05$).

Keywords: Aorta, stress ulceration, allopurinol, superoxide dismutase, oxygen-derived free radicals

Stress ulceration and pancreatic damage frequently occur after cardiovascular surgery, particularly when the thoracic aorta is cross-clamped[1]. The aetiology of gastric stress ulceration is poorly defined with ischaemia as a probable cause[2,3]. Another possible mechanism is the release of oxygen-derived free radicals during reperfusion of the stomach.

The aim of this study was to establish an animal model that mimics clinically severe gastric ischaemia with aortic cross-clamping followed by reperfusion. Three different methods of preventing tissue damage were tested, including the mechanical re-establishment of blood flow with a shunt, the biochemical prevention of ischaemia-induced injury with a calcium channel blocker (flunarizine), or the prevention of reperfusion injury with allopurinol or superoxide dismutase. Calcium influx during ischaemia and release of superoxide radicals during reperfusion of ischaemic tissue are believed to be mediators of tissue injury[4].

Methods

Thirty-two male Chacma baboons (*Papio ursinus*) of 13·6 to 26·8 kg body weight were immobilized with ketamine (2–3 mg/kg) and maintained under general anaesthesia by a continuous infusion of sodium thiopentone (Intraval Sodium, May and Baker) by a Harvard pump (Model 944A) at a rate of 5 mg/min. Catheters were inserted into the right atrium (for pressure measurement); the pulmonary artery (Swan-Ganz catheter for cardiac output measurement); the left atrium (for the injection of microspheres); proximal aorta (for aspiration of microspheres); and distal aorta (for pressure measurement below the aortic cross-clamp). The ventilation technique, haemodynamic monitoring, drug dosages and surgical technique have been described in detail previously[4,5]. The timing of operative procedures, drug administration, and blood flow measures have also been shown in detail diagrammatically[4]. The animals were divided into the following groups:

Control group (C, $n=5$). This group consisted of five animals in which no surgery was performed other than the insertion of catheters. Gastric and pancreatic blood flow was calculated by the radioactive microsphere method at the beginning of the experiments and 120 min later.

Aorta cross-clamp group (AX, $n=5$). These animals underwent thoracotomy and aortic cross-clamping for 60 min. The aorta was cross-clamped immediately below the subclavian artery and above the diaphragm. Blood-flow studies were done after thoracotomy (before aortic cross-clamping), 30 min after cross-clamping, 60 min after cross-clamping, and 30 min after the aorta was unclamped.

Shunt group (SH, $n=7$). In addition to cross-clamping, a 7 mm internal diameter shunt was immediately inserted after cross-clamping proximal and distal to the aortic clamps and kept open for 60 min. The mean cross-clamp period required for the insertion of the shunt was 21·6 ± s.e.m. 2·2 min. Blood flow studies were performed before cross-clamping, during cross-clamping, after 60 min of shunting, and 30 min after unclamping the aorta.

Flunarizine group (F, $n=5$). The procedure was as described for AX. However, 0·2 mg/kg of flunarizine (Janssen Pharmaceutica) was administered intravenously 10 min before cross-clamping, followed by a second dose 30 min after aortic cross-clamping. The second blood-flow study was done immediately before aortic cross-clamping, 10 min after the first dose of flunarizine. The timing and route of flunarizine injections were chosen to closely correspond to any possible clinical application.

Allopurinol group (ALL, $n=5$). This procedure was identical to AX with the exception that the baboons received a daily oral dose of 30 mg/kg of allopurinol for three days before the experiment.

Superoxide dismutase group (SOD, $n=5$). In this group the procedure was identical to ALL, including the use of allopurinol, but in addition, 5 min before unclamping the aorta, 25 mg of bovine Cu–Zn superoxide dismutase (minimal activity of 3000 units/mg, Pharmacia, Uppsala) was administered into the left atrium. A further dose of 25 mg was administered immediately on removal of the aortic cross-clamps.

In the groups described above, damage was assessed by naked-eye changes in the stomach, and indirect evidence of free-radical action was sought by measuring tissue concentrations of glutathione (GSH) and oxidised glutathione (GSSG). Oxygen-derived free radicals, together with glutathione peroxide as the catalyst, convert reduced GSH to GSSG; thus, the biochemical analysis of tissue GSH and GSSG levels should be indirect evidence of superoxide generation[6].

Blood flow was determined by 13 μm microspheres labelled with ^{51}Cr, ^{141}Ce, ^{46}Sc, and ^{103}Ru (New England Nuclear, Boston, MA). Approximately 1–2 million spheres in dextran 70 were mixed, using an MSE 5–78 Sonicator (MSE, Crawley, West Sussex, UK), and immediately injected into the left atrium at body temperature over a 10 s interval. Arterial reference samples were withdrawn from the proximal aorta at a constant rate of 12 ml/min for a period of 80 s starting 5 s before the microsphere injections. The withdrawn blood was weighed and the volume calculated (weight × 1·04). Blood and tissue samples were placed in vials, the tissues dissolved in hot nitric acid, and then counted in a well gamma counter. From the blood reference samples, tissue-blood flows were calculated on a computer by the method described by Heyman and Rudolph[7].

After the fourth blood-flow study, that is 30 min after the clamps were removed, the abdomen was opened and approximately 2 g of gastric mucosal specimens were taken from the gastric fundus, corpus, and antrum. They were immediately placed in liquid nitrogen and stored at −70°C for later biochemical analysis. The animals were then killed with an intra-atrial injection of concentrated potassium chloride. The stomach was then extracted and opened along the greater

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curvature and divided into 1 cm squares. Each was examined for lesions and defined as macroscopic haemorrhages, superficial erosions, or ulcers. The sum of segments with lesions was expressed as a percentage of the total number of grid squares as proposed by Itoh and Guth[8].

The gastric mucosa was separated from the underlying muscle, individually weighed, and the blood flow determined for each segment of gastric mucosa and muscle.

In the control group and in the groups where superoxide radicals were thought to play a role in damage (XC, ALL and SOD), gastric specimens were taken, as described above, for biochemical analysis. The specimens were later analysed for total GSH and GSSG content as suggested markers of superoxide radical formation[9]. Adams *et al.*[10] described the biochemical technique that was used. For GSSG determination, frozen samples were homogenized in 10 mM N-ethylmaleimide (Merck) to prevent artificial oxidation. To determine total GSH (GSH + GSSG) levels, the samples were homogenized in 20 mM 5,5′-dithiobis(2-nitrobenzoic acid, Sigma) to convert all GSH to GSSG.

Results are expressed as means ± s.d. unless otherwise stated. Nonparametric methods (Wilcoxon test for paired samples, Mann–Whitney *U* test, and Fisher exact test) were used for statistical analysis.

The study was approved by the University of the Witwatersrand Senate Animal Ethics Committee.

Results

During aortic cross-clamping, the mean abdominal aortic pressure was between 12 ± 2 mmHg at the beginning of aortic cross-clamping and 6 ± 3 mmHg at the end of aortic cross-clamping[6]. While the shunt was open, the distal aortic pressure started at 94 ± 13 mmHg and slowly decreased to 72 ± 15 mmHg at the end of shunting[6].

The gastric blood flow results are shown in *Figure 1*. There was no difference in the basal mucosal blood flow between the groups. Blood flow fell with aortic cross-clamping and improved with shunting in group SH ($P < 0{\cdot}05$). With reperfusion, increased blood flow was noted in the allopurinol group ($P < 0{\cdot}001$ *versus* control, $P < 0{\cdot}05$ *versus* basal) and particularly in the flunarizine group ($P < 0{\cdot}001$ *versus* control, $P < 0{\cdot}001$ *versus* basal). Before cross-clamping there was no effect of flunarizine on gastric mucosal blood flow.

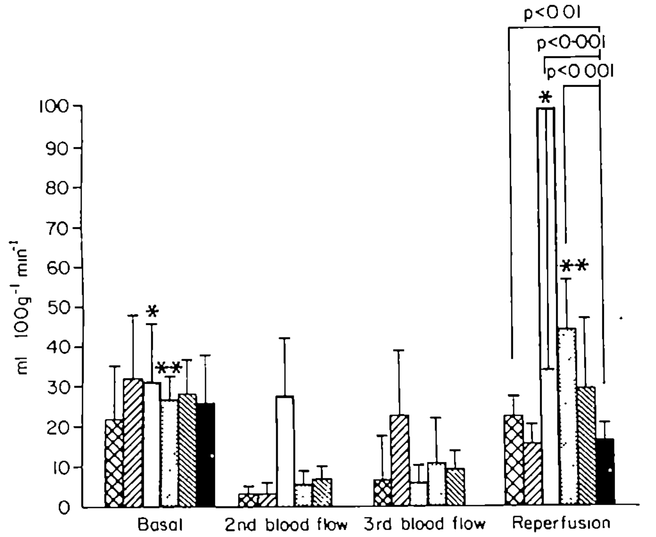

Figure 1 *Gastric mucosal blood flow (ml/100 g/min) in the groups studied:*

▩ *aorta cross-clamped* ■ *control*
▨ *shunt*
□ *flunarizine*
⊡ *allopurinol*
▨*superoxide dismutase*

Note that the second blood flow in the flunarizine group was before aortic cross-clamping, and the third blood flow in the shunt group was after the shunt was opened. The asterisks denote comparison between basal and reperfusion blood-flow levels (= flunarizine,* $P < 0{\cdot}001$*; ** = allopurinol,* $P < 0{\cdot}05$*)*

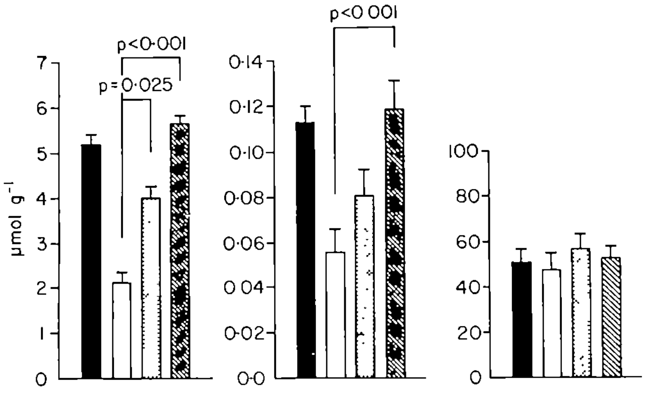

Figure 2 *Gastric mucosal total GSH (left), GSSG (centre) and GSH/GSSG ratio (%) (right) in the various groups.* ■, *Control;* □, *aorta cross-clamped;* ⊡, *allopurinol;* ▨, *superoxide dismutase*

At the end of the experiments no gastric lesions were found in the control group. A mean of 38 ± 18 per cent (mean ± s.e.m.) gastric lesions was found in the AX group, 7 ± 3 per cent in the shunted group ($P = 0{\cdot}02$ *versus* AX), 5 ± 3 per cent in the allopurinol group ($P = 0{\cdot}03$ *versus* AX), and none in the SOD group ($P = 0{\cdot}004$ *versus* AX). Flunarizine caused severe diffuse haemorrhagic erosions or ulcers in all segments of the stomach ($P < 0{\cdot}01$ *versus* AX).

The results of the biochemical analyses of the gastric mucosa are shown in *Figure 2*. GSH levels were lowest in the cross-clamped group ($P < 0{\cdot}001$) and depressed in the allopurinol group ($P < 0{\cdot}05$) in comparison with the control and SOD groups. There was no difference between the control group and the SOD group. Similar results were obtained for GSSG levels. The GSSG/GSH ratio did not alter.

Discussion

This study has shown that allopurinol, superoxide dismutase, or a shortened time of severe gastric ischaemia (SH group), reduces the severity of gastric lesions after aortic cross-clamping. Superoxide dismutase combined with allopurinol had an additive effect in completely preventing gastric lesion formation. In addition, the combination prevented the loss of GSH from the gastric mucosa. Furthermore, gastric mucosal lesion formation was associated with a reperfusion hyperaemia in the most severely damaged stomachs. The untreated cross-clamp group had the greatest loss of GSH and GSSG.

Organ protection by allopurinol or superoxide dismutase (SOD) during reperfusion of tissues is well documented[8,11–13]. Itoh and Guth[8] have shown that allopurinol or SOD significantly protect the gastric mucosa in haemorrhagic shock experiments with hydrochloric acid gastric perfusion. They showed that allopurinol reduced the area of lesions significantly more than SOD did. In the present study, we have shown that the combination of allopurinol with SOD completely prevented gastric lesion formation induced by severe gastric ischaemia. We are not aware of this additive effect of allopurinol and SOD having been described previously. Current evidence suggests that with ischaemia, the levels of gastric adenosine triphosphate (ATP) are reduced[3]. The end product of ATP breakdown in ischaemic tissues is hypoxanthine[13]. Furthermore, during ischaemia xanthine dehydrogenase is converted to xanthine oxidase[13]. When reperfusion occurs in a reaction catalysed by xanthine oxidase, oxygen combines with hypoxanthine to form superoxide radicals[13]. These superoxide radicals are scavenged by SOD, which catalyses their dismutation to hydrogen peroxide. Allopurinol inhibits xanthine oxidase and thereby decreases the formation of superoxide radicals[13]. However, this is not the only pathway for free radical generation, and so any radicals that may be formed by alternative pathways can be scavenged by SOD. This may be the explanation for the additive effect we have observed with the combination of allopurinol and SOD in preventing superoxide radical-associated gastric lesions.

The severe haemorrhagic lesions in the entire stomach of animals treated with flunarizine was surprising considering its reported cytoprotective effect[14], vascular antispasmodic effect[15], and reported prevention of the decrease of red blood cell pliability that occurs during hypoxia[16]. Verapamil, a different calcium channel blocker, has been shown to protect the small intestine against ischaemic damage[17]. The postulated mechanism of this protection is that the conversion of xanthine dehydrogenase to xanthine oxidase is inhibited during ischaemia. During ischaemia the influx of calcium into cells is believed to be an important mechanism of tissue injury. Hence, verapamil also may have prevented tissue injury by this mechanism. Whether flunarizine has a similar effect is unknown. Hossmann *et al.*[18], using flunarizine, failed to prevent the post-ischaemic tissue accumulation of calcium ions. or improve biochemical recovery. Dean *et al.*[19] noted the failure of lidoflazine, a drug closely related to flunarizine, to protect against neurological ischaemia. Newberg *et al.*[20] also noted that flunarizine caused severe pulmonary oedema in experimental animals, although this was not encountered. Paraplegia could not be prevented after aortic cross-clamping with flunarizine, and a severe reperfusion hyperaemia also occurred in the spinal cord. A similar severe hyperaemia after ischaemia was noted in the small bowel, large bowel, and pancreas[21]. It is possible to speculate that the vasodilatory effect of flunarizine plays a role in increasing the in-flow pressure of blood into ischaemic tissues, and combined with the endothelial damage caused by oxygen-derived radicals, greater extravasation of blood occurs, finally leading to haemorrhagic lesions.

Where a shunt was placed during a short ischaemic period of aortic cross-clamping, the rapid re-establishment of blood flow through the shunt reduced the incidence of lesions. With a reduced length of time of severe ischaemia, less of the hypoxanthine substrate would have been available for the conversion of oxygen to superoxide radicals. While the stress of surgery alone may have been sufficient to cause gastric lesions, this does not appear to have been a major factor in the aetiology of the gastric lesions. The reduced time of ischaemia in the shunt group reduced the incidence of lesions, despite the shunt adding to the stress induced by surgery.

In most previous models of gastric stress lesion formation, it has been necessary to add luminal HCl in addition to ischaemia to produce lesions. This experiment used a haemorrhagic shock model in baboons with the addition of luminal HCl to produce gastric mucosal lesions after partial ischaemia (C. M. Von Ritter, M. M. J. Oosthuizen, L. G. Svennson, S. Hunter, H. Lambrecht and R. A. Hinder, unpublished results). However, in this present model with severe gastric ischaemia there was only the endogenous secretion of acid. The reason for the greater success in inducing gastric lesions in this model may be because the baboon, as in the case in man, is an interdigestive gastric acid secretor[22]. Although pH in the stomach was not measured in this study, previous studies have shown that the baboon's stomach is acidic under basal conditions[22]. Thus, this model is closer to the clinical situation than previous studies in dogs and rats. The association of reperfusion hyperaemia with gastric lesions is interesting. It is believed that superoxide radicals, possibly released from granulocytes adhering to the vascular endothelium, cause damage to the endothelium and lipid membranes[12]. This could result in a loss of tone of the arterioles and the precapillary sphincters, with a greater initial in-flow of blood into the ischaemic tissues during reperfusion. We noted a similar hyperaemia in the spinal cord which was associated with paraplegia[6,7].

The decreased levels of GSH in the gastric mucosa in the group with prolonged ischaemia during cross-clamping would suggest that superoxide radicals were produced. This would explain the higher incidence of gastric lesions in this group. Similarly, in the allopurinol group, with xanthine oxidase inhibition, GSH levels were not as low as the cross-clamped group, and the number of gastric lesions was also fewer. Comparison of the SOD group with the control group shows that there was no difference in GSH and GSSG levels, neither were any lesions formed in this group, suggesting that allopurinol had inhibited xanthine oxidase and whatever free radicals were formed were scavenged by SOD. As GSSG levels should theoretically increase with oxidative stress, increased levels of GSSG in the mucosa of cross-clamped animals (AX) with an increased GSSG/GSH ratio would have been expected. Nevertheless, this did not occur. There is evidence that active transport of GSSG out of cells may be an emergency mechanism to protect cells from the toxic effects of GSSG[9]. Another possible explanation is that the lower levels of GSSG (and GSH) are due to their leakage from damaged cells or indicate cellular damage with cellular sloughing into the gastric lumen. Thus tissue levels of GSH and GSSG are possibly not reliable indicators of superoxide radical generation in the stomach as has previously been thought.

This study has shown that severe gastric mucosal ischaemia alone followed by reperfusion produces gastric mucosal lesions in baboons. The duration of ischaemia is important. The gastric lesions appear to be associated with oxygen-derived free radicals since allopurinol and SOD prevented the formation of these lesions. Furthermore, the combination of allopurinol and SOD had an additive effect in preventing lesion formation. The researchers are currently investigating the possible use of SOD in human subjects.

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Case report

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Dumping syndrome following anterior lesser curve seromyotomy with posterior truncal vagotomy

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Postoperative dumping following anterior lesser curve seromyotomy with posterior truncal vagotomy has not been reported before.

Case report

A 19-year-old man presented with a perforated anterior duodenal ulcer which was oversewn and then treated by anterior lesser curve seromyotomy with posterior truncal vagotomy 3 months later. After 6 months he had his first grand mal epileptic fit for which there was no obvious cause. Since the operation he had had three episodes of light-headedness and sweating about 4 hours after meals, all of which resolved spontaneously. Abdominal and neurological examination was normal at the time of this presentation, and an electroencephalogram was also normal. A radionuclide gastric emptying test showed marked early emptying with 55 per cent of the meal leaving the stomach in the first 10 min (normal upper limit 28 per cent by 10 min) although there was preservation of the solid–liquid differential. An initial oral glucose tolerance test, with $\frac{1}{2}$ h blood samples, demonstrated hypoglycaemia (2·1 mmol/l) at 1 h but no prior rise in blood glucose concentration; a second test, with a 15 min blood sample, detected an early rise (fasting 3·9 mmol/l; 15 min after glucose, 7·8 mmol/l) followed by hypoglycaemia (2·8 mmol/l) at 2·5 h. An insulin stress test demonstrated a response in gastric acid secretion (basal hour 248 ml with 17·4 mmol of acid; 60–120 min after insulin 268 ml with 33·6 mmol of acid) which was similar to the response after a pre-operative pentagastrin test. An upper gastrointestinal endoscopy showed minor distortion of the pylorus and duodenal cap but no peptic ulceration.

The patient was treated with small frequent meals of low carbohydrate content and he has had no further fits or features of hypoglycaemia over the last 5 years.

Discussion

It is likely that this patient's episodes of post-prandial light-headedness and sweating after surgery constituted a dumping syndrome in view of the associated rapid gastric emptying and hypoglycaemia following oral glucose. However, it is unusual for accelerated gastric emptying to occur when there is persisting vagally mediated acid secretion. The possibility that this patient had accelerated gastric emptying pre-operatively cannot be excluded, but he had no symptoms before surgery to suggest this.

Theoretically, both highly selective vagotomy and anterior lesser curve seromyotomy with posterior truncal vagotomy are unlikely to produce dumping syndrome as antropyloric motor function is preserved. However, highly selective vagotomy has been reported to have a 6 per cent incidence of dumping syndrome at 1 year[1]. Anterior lesser curve seromyotomy with posterior truncal vagotomy has the advantage of being easier to perform and although previous gastric emptying studies have shown accelerated emptying of liquids after surgery[2] there has been no report of the dumping syndrome in over 600 operations[3]. Although this patient exhibits dumping, it must be extremely rare with an incidence of around 0·17 per cent.

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Perforated duodenal ulcer managed by simple closure versus closure and proximal gastric vagotomy

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A prospective randomized trial of simple closure versus *closure and proximal gastric vagotomy was conducted in 50 consecutive patients with perforated duodenal ulcer. There was one postoperative death in each group and no difference in postoperative morbidity. After a median follow-up of 54 months (24–96) the cumulative recurrence rate after simple suture was 52 per cent against 16 per cent after proximal gastric vagotomy and closure* ($P<0\cdot01$)*. The recurrence rate after proximal gastric vagotomy for perforated duodenal ulcer was comparable to the recurrence rate seen after the electively performed operation.*

Keywords: Duodenal ulcer, perforation, proximal gastric vagotomy

Recurring ulcer symptoms requiring treatment after simple closure for perforated duodenal ulcer occur in 40–80 per cent of patients[1–4], which before the introduction of the histamine-H_2 blockers resulted in a reoperation rate of up to 60 per cent[3,5]. Today a number of these patients probably can be managed satisfactorily with medical treatment, but it is still not known whether patients with perforated ulcer suffer from a particularly aggressive type of ulcer disease and hence whether medical treatment will be less successful than in other ulcer patients. Consequently definitive surgery for perforated duodenal ulcer is still an attractive alternative provided the procedure can be performed safely, which means no increased operative mortality or morbidity compared to simple closure, and a cure rate which equals that achieved after elective surgery.

Controlled trials on the effect of definitive surgery for perforated duodenal ulcer are few. In a recent trial it was demonstrated that truncal vagotomy and drainage (TV) was clearly superior to simple closure in terms of cure rate and persisting symptoms, and that the procedure could be performed without mortality and without increased morbidity[4]. The same was true in another trial on chronic duodenal ulcer where one-third of the patients were allocated to TV; in this study one-third of the patients had a proximal gastric vagotomy without drainage (PGV) and one-third a simple closure[6]. Also PGV could be performed without mortality and with no increased operative morbidity and with a lower rate of persisting symptoms than TV.

The aim of the present controlled trial has been to compare the outcome of simple closure and closure combined with PGV for perforated duodenal ulcer in a consecutive series of patients irrespective of the length of their ulcer history.

Patients and methods

Fifty consecutive patients, 23 men and 27 women, with a median age of 48 years (range 12–63) entered the trial during the years 1978–83. Patients were included irrespective of the length of history of their ulcer disease since any limit must be arbitrary and since the validity of such information in severely ill patients often will be unreliable. It was not registered whether the patients were treated pre-operatively with anti-ulcer drugs. Patients with one or more of the following criteria were excluded: age >70 years, duration of perforation >24 h, pyloric stenosis or previous ulcer surgery. By random numbers 25 patients were allocated to simple closure and 25 to closure combined with PGV. No patients suffered from serious concurrent disease and none were in shock pre-operatively. Median follow-up was 56 months (range 23–85). Endoscopy was performed in all patients who at any time after the operation had symptoms suggestive of ulcer disease. The following patients were classified as having recurrence; all patients operated for recurrent ulcer, patients who had an ulcer diagnosed by endoscopy or patients who had received medical treatment with anti-ulcer drugs for more than one period. Results are given as percentages with 95 per cent confidence limits. Differences were evaluated by Fisher's exact test.

Results

No intra-operative complications such as splenic damage occurred. Postoperatively one patient died after PGV from myocardial infarction and one after simple closure from peritoneal sepsis. Autopsy showed that the closure leaked and the death of this patient must be considered to be due to a technical failure (*Table 1*). Five non-fatal postoperative complications occurred after PGV (20 per cent, 7–41) and two after simple closure (8 per cent, 1–26) ($P>0\cdot05$). One patient with subphrenic abscess was treated conservatively and had an uneventful recovery but died one year later of pulmonary carcinoma, and one patient with a leakage of the ulcer closure was re-operated on the fourth postoperative day and also recovered uneventfully.

Forty-five patients were re-examined, three patients had died of causes unrelated to their ulcer disease, one developed a Zollinger–Ellison syndrome and one was lost to follow-up. After PGV and closure four patients developed recurrent ulcer (16 per cent, 3–36) and after simple closure thirteen developed recurrence (52 per cent, 31–72) ($P<0\cdot01$). Nine patients with recurrence after simple closure were re-operated (69 per cent, 38–90), eight had an elective PGV owing to unsatisfactory management on H_2-blocker treatment and one had a PGV and closure for a re-perforation 6 months after the first operation. Three of four patients with recurrence after PGV and closure have been managed satisfactory on H_2-blocker treatment, and one patient with persistent symptoms has refused further surgery.

All patients operated electively for recurrence and five patients who received medical treatment had the recurrent ulcer diagnosed endoscopically. Three patients were classified as having recurrence based on a history of ulcer symptoms which had required treatment with anti-ulcer drugs for at least two periods. None of the patients with recurrent ulcer presented with haematemesis and only the patient with perforation presented as an emergency case. There were no cases of pyloric stenosis. Results at follow-up according to Visick's classification are

Table 1 *Postoperative complications*

	Proximal gastric vagotomy and closure	Simple closure
Myocardial infarction	1*	—
Peritoneal sepsis	—	1*
Pulmonary infection	1	1
Wound infection	2	1
Subphrenic abscess	1	—
Leakage	1	—

*Died

Table 2 *Visick score after operation for perforated duodenal ulcers*

	Visick grade				
	I	II	III	IV	Excellent/good
Simple closure	3	3	4	13	26 per cent $P<0{\cdot}01$
Proximal gastric vagotomy	10	7	1	4	77 per cent

shown in *Table 2*; 77 per cent (55–92) obtained excellent or good results after PGV compared with 26 per cent (10–48) after simple closure ($P<0{\cdot}01$). No long term sequelae were documented in either group.

Discussion

This study has shown that PGV and closure for perforated duodenal ulcer can be performed as safely as simple closure. The gain has been obvious with respect to recurrent ulceration and the recurrence rate after PGV did not exceed the rate after electively performed PGV demonstrated in a controlled study from our department[7,8]. Other series have reported lower recurrence rates after PGV for perforated duodenal ulcer[6] but since recurrence rates also differ markedly in elective series[7,9,10] it may be more relevant to compare the recurrence rate after acutely performed PGV with the recurrence rate obtained in the same department when the procedure is performed electively. In the only controlled trial on PGV for perforated duodenal ulcer[6] the recurrence rate was 3·8 per cent which is far below rates reported in most elective series and is probably partly due to a short follow-up. In an uncontrolled study on PGV for perforation in chronic duodenal ulcer disease the recurrence rate was 20 per cent after a median follow-up of 49 months which is comparable to the present series[11].

Some studies on definitive surgery for perforated duodenal ulcer only include patients with chronic ulcer disease often defined by a history >3 months[6,11]. In one of these studies[11] recurrence after PGV in patients with a history >3 months was equal to the recurrence rate found after simple closure in patients with a history <3 months; since, however, this was an uncontrolled study the conclusion must be considered with some caution. We find such arbitrary limits for the patients' history less relevant for the decision on choice of treatment unless subsequent studies show a difference in the natural history of duodenal ulcer disease complicated with perforation related to the duration of the disease before perforation. There is no obvious explanation of the unusual sex ratio in this study which differs markedly from the ratio in our elective series[7].

It could be argued that the routine use of PGV and closure for perforated duodenal ulcer might cause 43 per cent of the patients to have an unneccessary PGV. This will of course only be acceptable if, as shown in this study, PGV and closure can be performed as safely as simple closure, i.e. without increased early or late morbidity and with a recurrence rate comparable to the rate obtained after electively performed PGV.

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Effect of duodenogastric reflux on gastric mucosal proliferation after gastric surgery

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The effect of duodenogastric reflux on cell proliferation and mucosal mass in the stomach was studied. Male Wistar rats ($n=118$) *were submitted to Polya partial gastrectomy, partial gastrectomy with Roux-en-Y diversion of bile, total duodenogastric reflux or handling of the stomach alone (sham operation). Following oral administration of the carcinogen* N*-methyl-*N′*-nitro-*N*-nitrosoguanidine for 6 months, animals were killed 6, 9 or 12 months postoperatively and their stomachs were examined for crypt cell production rate and mucosal DNA content. Compared with shams, crypt cell production rate was more than twice as high in the gastric remnant 12 months after Polya partial gastrectomy* ($P<0\cdot001$) *and median DNA content was 31 per cent greater* ($P=0\cdot05$)*. After total duodenogastric reflux, DNA content was 62 per cent greater than in shams* ($P=0\cdot02$)*, while Roux-en-Y diversion reduced crypt cell production rate by 65 per cent* ($P<0\cdot001$)*. Only Polya gastrectomy increased the number of rats developing gastric carcinomas (9* versus *2 shams;* $P<0\cdot05$)*. Increased mucosal cell proliferation in rats with duodenogastric reflux may help to explain the development of gastric stump cancer.*

Keywords: Cell cycle, duodenogastric reflux, stomach neoplasms

Peptic ulcer surgery may predispose to the later development of gastric cancer[1,2], although this remains controversial[3]. Clinical studies have failed to define which operation carries the highest risk. Some suggest Billroth II resection[1,4], but Caygill and co-workers have recently shown that the risk appears highest after vagotomy and drainage procedures for duodenal ulcer and after Billroth II resection for gastric ulcer[2].

Both duodenogastric reflux[5,6] and hypochlorhydria[7,8] have been implicated in the aetiology of gastric stump cancer, but their relative roles are unclear. Duodenogastric reflux follows each of these operations, especially the Polya (Billroth II) gastrectomy, and premalignant histological changes are more common[6] and more severe[9] with increasing degrees of reflux. Since Roux-en-Y diversion of bile leads to a reduction in mucosal dysplasia[10] and foveolar hyperplasia (elongation and tortuosity of the gastric pits)[11] and protects against experimental carcinogenesis[12,13], duodenogastric reflux of bile may be more important than hypochlorhydria in the aetiology of gastric stump cancer. In support, bile acids potentiate gastric carcinogenesis in rats[14] and increasing degrees of duodenogastric reflux have a similar effect[15].

Atrophic gastritis, intestinal metaplasia and dysplasia are all associated with gastric carcinogenesis[16–18], and gastric epithelial proliferation accompanies these premalignant mucosal changes[19–21]. Since increased cell proliferation promotes carcinogenesis in the colon[22] and the pancreas[23], we have studied the effect of duodenogastric reflux on cell proliferation and mucosal mass in the stomach.

Materials and methods

Experimental animals

One hundred and eighteen male Wistar rats underwent either a sham operation ($n=30$), Polya (Billroth II) partial gastrectomy ($n=30$), total duodenogastric reflux ($n=28$) or partial gastrectomy with Roux-en-Y biliary diversion ($n=30$) (*Figure 1*). The animals, weighing 100–125 g, were received into the animal house one week before the start of the experiment. After operation, food (Oxoid Breeding Diet, Styles, Bewdley, Worcestershire, UK) was withheld for the first 24 h and was then available *ad libitum*; water was allowed throughout. Animal quarters were lit in alternate 12-hourly cycles and rats were weighed weekly throughout the experiment. Two weeks postoperatively the carcinogen *N*-methyl-*N′*-nitro-*N*-nitrosoguanidine was added to the drinking water (75 μg/ml) and administered continuously thereafter for 6 months. *N*-methyl-*N′*-nitro-*N*-nitrosoguanidine was made up twice weekly from a stock solution containing 1 mg/ml, which was stored refrigerated in the dark and was given in water bottles protected from the light by black PVC to prevent degradation.

Surgical operations (Figure 1)

These were performed under light ether anaesthesia. Sham operated animals had a laparotomy with handling of the stomach and jejunum and acted as controls. Polya gastrectomy was performed by removing the distal half of the glandular stomach with reconstruction by an iso-peristaltic, antecolic gastrojejunostomy. Total duodenogastric reflux was induced by a modification of the Schmilinsky procedure, an operation originally used for the treatment of peptic ulceration[24] but quickly abandoned because of its complication rate. Distal hemigastrectomy with Roux-en-Y biliary diversion was performed with a jejuno-jejunal anastomosis 4 cm from the gastric anastomosis. Continuous 6/0 silk sutures were used for all anastomoses, and at the end of each operation 0·25 mg vitamin K was given subcutaneously to prevent postoperative bleeding.

Autopsy specimens

At 6, 9 and 12 months after operation six rats from each group were killed and submitted to autopsy. Each animal was given an intraperitoneal injection of vincristine sulphate (1 mg/kg body weight) at intervals from 30 to 180 min before death, for stathmokinetic studies[25]. The stomachs were excised, opened along the greater curve and washed clean with ice-cold saline. In a glass tray over crushed ice a 1 cm^2 of stomach body was excised and the mucosa was scraped off to provide a mucosal pellet, which was immediately frozen in liquid nitrogen at −70°C for later DNA estimation. Small samples of the remaining body of the stomach and antrum (if present) were taken and fixed in Carnoy's solution for 4–6 h and then transferred to 70 per cent alcohol for later crypt cell production rate estimation. Surviving animals

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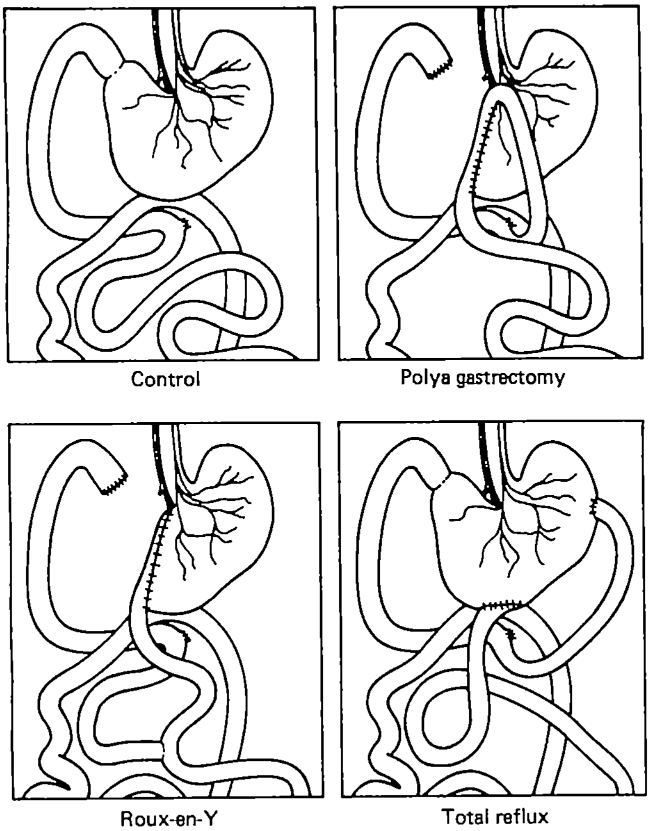

Figure 1 *Operative groups*

were killed 15 months postoperatively and autopsied for tumour yield alone.

Crypt cell production rate

Specimens were stained with Schiff's reagent by Feulgen's method. On a glass slide, under the dissecting microscope, the mucosa was teased from the submucosa and individual glands were dissected out. A drop of 45 per cent acetic acid was applied and the glands were gently squashed under a cover-slip. The slide was transferred to a light microscope for examination. Arrested metaphases in each gland were counted, and the mean of counts from 10 individual glands was taken as the value for that gastric specimen at that time. Crypt cell production rate was determined by calculating the slope of the line best fitting the 6 individual points thus obtained by linear regression analysis.

DNA measurement

DNA was measured by a simplified method first described by Scott *et al.*[26] and modified by Hinrichs *et al.*[27], which relies on alkaline digestion to separate the two nucleic acids. Aliquots of frozen, weighed, homogenized specimens were treated with ice-cold 25 per cent trichloracetic acid. The precipitate was washed with ice-cold alcoholic 0·1 M potassium acetate and then with absolute alcohol for 30 min at 60°C. After overnight drying at 37°C, pellets were dissolved in 1 M potassium hydroxide at 85°C. DNA was measured fluorimetrically by a modification of the method of Kissane and Robbins[28], which is specific for this compound.

Statistical analysis

Crypt cell production rate regression lines were compared, and the significance of the difference between their slopes was assessed by Student's t test. Kruskal–Wallis analysis of variance and the Mann–Whitney U test were used for animal weights and DNA levels, and the χ^2 test with Yates' correction was used for tumour yields.

Results

Weight gain

All animals initially lost weight postoperatively but this was regained in 2–3 weeks. Control animals gained most weight over the study period and at 12 months their median weight was 539·5 g (range 427–647 g). Animals undergoing Polya gastrectomy (468·5 g, range 411–547 g) and Roux-en-Y (462 g, range 425–541 g) weighed less than controls but the differences were not significant. Total duodenogastric reflux animals weighed 28 per cent less than controls (389 g, range 328–414 g; $P=0\cdot008$).

Gastric mucosal DNA (Figure 2)

At 6 months gastric mucosal DNA levels were lower in the three experimental groups (particularly total duodenogastric reflux) compared with shams but these differences were not significant. By 12 months DNA levels were 31 per cent higher after Polya gastrectomy than in control stomach (837 *versus* 637 μg/cm^2; $P=0\cdot05$), and after total duodenogastric reflux DNA content (1032 μg/cm^2) was 62 per cent greater ($P=0\cdot02$). By contrast, Roux-en-Y biliary diversion had no significant effect on gastric mucosal DNA (703 μg/cm^2). Comparing DNA levels at 6 months with those at 12 months there were no significant changes among shams or those with Roux-en-Y biliary diversion. After Polya gastrectomy, however, the median DNA level increased by 30 per cent ($P=0\cdot01$) and after total duodenogastric reflux it increased by a factor of three ($P=0\cdot001$).

Crypt cell production rate

In the gastric body, crypt cell production rate increased between 6 months and 12 months in 3 of 4 groups, though not all changes reached significance (*Figure 3*). There was a 66 per cent increase for controls ($P<0\cdot02$) and a 142 per cent increase after Polya gastrectomy ($P<0\cdot001$). By contrast, crypt cell production rate diminished by 55 per cent ($P<0\cdot001$) in rats with antrectomy and Roux-en-Y biliary diversion. In the gastric antrum over the same period the increase in controls did not quite reach significance. A 180 per cent increase was recorded for rats with total reflux ($P<0\cdot01$) (*Figure 4*).

At 6 months Polya gastrectomy had increased crypt cell production rate in the gastric body remnant by 71 per cent over control values (n.s.); by 9 months the increase was 75 per cent ($P<0\cdot05$) and by 12 months 149 per cent ($P<0\cdot001$) (*Figure 3*). By contrast Roux-en-Y diversion reduced crypt cell production rate to a third of control values at 12 months ($P<0\cdot001$). From

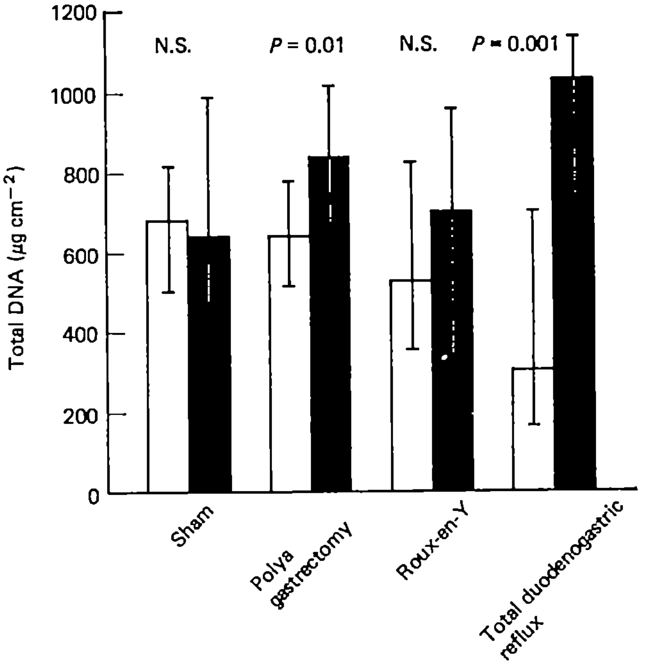

Figure 2 *Mucosal DNA levels in the gastric body at 6* (□) *and 12* (■) *months after operation.* (*Medians with ranges, Kruskal–Wallace analysis of variance and Mann–Whitney* U *test*)

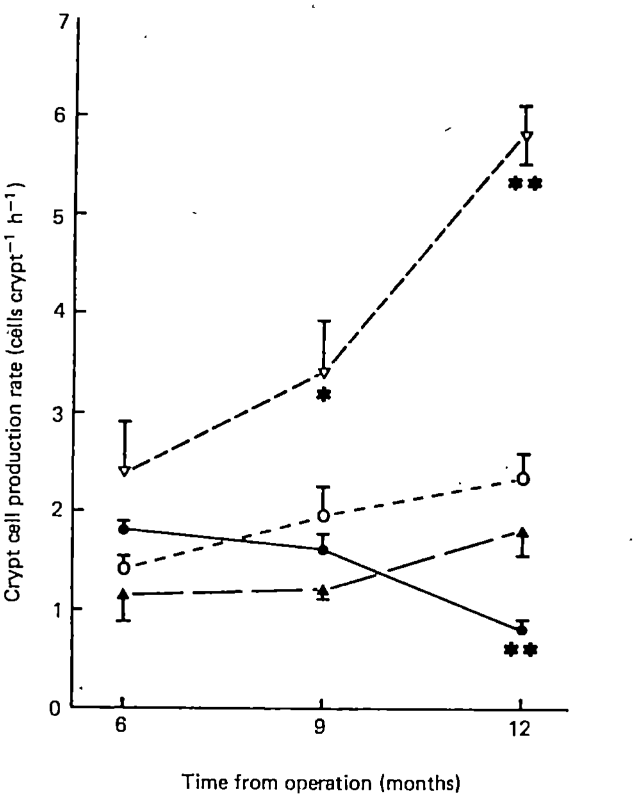

Figure 3 *Crypt cell production rates in stomach body. Controls* (○) *versus Polya gastrectomy* (▽), *Roux-en-Y* (●) *and total duodenogastric reflux* (▲). $^{*}P<0.05$; $^{**}P<0.001$

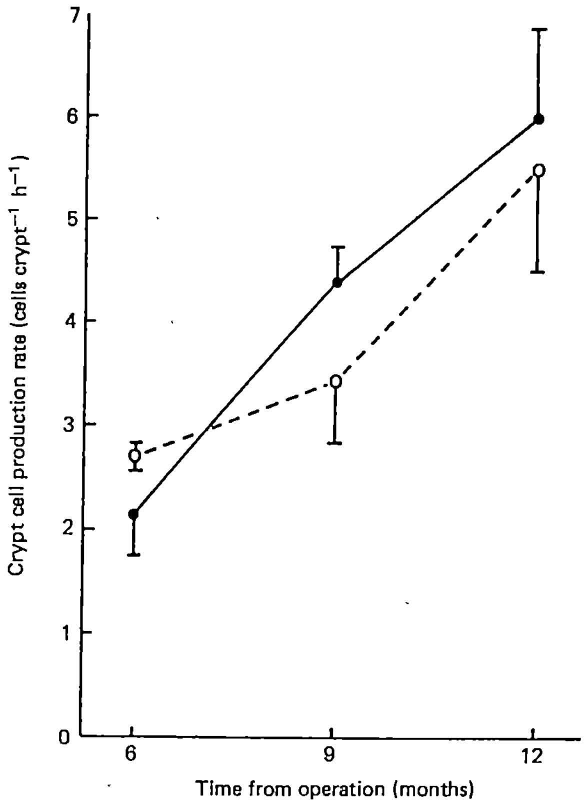

Figure 4 *Crypt cell production rates in stomach antrum.* ●, *Total duodenogastric reflux;* ○, *controls*

9–12 months after total duodenogastric reflux crypt cell production rate was higher in the antrum and lower in the body than in controls, although these differences did not attain statistical significance (*Figure 4*).

Tumour yield

Two control animals developed gastric adenocarcinomas at 12 months after operation. By contrast, 9 animals with Polya gastrectomy developed carcinomas in the gastric remnant at 12–15 months onwards ($\chi^2=4$; $P<0.05$). Four squamous cell carcinomas were found in the gastric rumen of rats undergoing total duodenogastric reflux, but there were no tumours at all in rats undergoing Roux-en-Y diversion of bile.

Discussion

This study has confirmed that operations on the stomach have a profound effect on cell proliferation in the gastric mucosa. The results show that both mucosal mass (DNA content) and cell proliferation (crypt cell production rate) are increased by duodenogastric reflux. Within 6 months of operation the DNA content of the mucosa was unchanged, but by 12 months it was 30–60 per cent higher in the two groups of rats with induced duodenogastric reflux. Crypt cell production rate increased over the study period in all animals except those with Roux-en-Y biliary diversion, probably as the result of the cumulative exposure to carcinogen; colonic carcinogens certainly stimulate cell proliferation[29]. The fall in crypt cell production rate seen after bile diversion could reflect loss of the tropic effect of gastrin following antrectomy[30]. If so, loss of gastrin in animals with partial gastrectomy was more than compensated for by the stimulatory effect of the increase in duodenogastric reflux. Although Polya gastrectomy progressively increased gastric crypt cell production rate, total duodenogastric reflux did not; likewise adenocarcinomas did not occur in the rats with total reflux. These animals weighed substantially less than those in the other groups, and although food intake was not measured it is likely to have been lower. In the intestinal tract hypophagia and weight loss can cause hypoplasia and reduced susceptibility to cancer[31,32], and the same could well apply to the stomach. Furthermore, this operation is known to cause hypergastrinaemia[22] and N-methyl-N'-nitrosoguanidine is inactivated in an acidic environment[34].

Previous studies using labelling techniques have also shown an increase in cell proliferation after gastric surgery, and chronic gastritis has been proposed as one of the causal factors[21,35,36]. Perhaps our DNA measurements merely reflect this chronic inflammatory response to duodenogastric reflux[37], but if so changes might have been anticipated within 6 months. Whatever the explanation, the DNA content of the mucosa correlated well with crypt cell production rate, which is an index of cell proliferation within the glandular proliferative zone. Along with the increments in both mucosal DNA and crypt cell production rate, Polya partial gastrectomy caused a fourfold increase in the number of gastric adenocarcinomas. After total duodenogastric reflux no adenocarcinomas were seen, but the development of squamous carcinomas in the gastric rumen presumably reflects severe irritation from bile.

In summary duodenogastric reflux increases cell proliferation and potentiates carcinogenesis in the gastric mucosa of rats receiving N-methyl-N'-nitrosoguanidine. Although the results cannot necessarily be extrapolated to man, they could well implicate duodenogastric reflux in the pathogenesis of gastric cancer after operation for peptic ulcer disease.

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Fine-needle aspiration biopsy and the diagnosis of thyroid cancer

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Conventional criteria for the evaluation of thyroid nodules are inaccurate in identifying the small proportion of malignant neoplasms. The diagnostic accuracy of fine-needle aspiration biopsy (FNAB) for cytology was therefore assessed in 562 patients with nodular thyroid disease, 373 of whom (66·4 per cent) had histological confirmation of the cytological diagnosis. Sixty-one aspiration biopsies were positive for malignancy, and the diagnosis was confirmed histologically in 59 of these (96·7 per cent). Thus, there were two false positive cytology results among 310 patients with proven benign disease (0·6 per cent). Four of sixty-three patients with proven carcinoma had a benign cytological diagnosis, a false negative rate of 6·3 per cent. In 57 of the 59 malignancies (96·6 per cent) correctly diagnosed by FNAB the histological type of tumour was successfully identified. Overall 367 of 373 patients received correct cytological discrimination between benign and malignant nodules, an overall accuracy of 98·4 per cent for FNAB. The sensitivity of the test was 93·7 per cent and the specificity 99·4 per cent. Besides being safe, cost-effective and reliable, FNAB directs the appropriate selection of patients for surgery and enables the correct operation to be performed for each type of tumour.

Keywords: Thyroid, carcinoma, fine-needle aspiration biopsy, cytology

A 'solitary' nodule is a common presentation of thyroid disease, occurring in some 3 per cent of the British population[1]. By contrast thyroid cancer is rare, accounting for less than 0·5 per cent of all new malignancies annually registered in England and Wales[2] and less than 0·5 per cent of all cancer deaths[3]. Only between 6 and 14 per cent of operations for thyroid nodules yield a diagnosis of cancer[4,5].

The essential challenge in the management of patients with nodular thyroid disease is to identify the few malignant tumours among the large number of benign lesions. Conventional criteria are inefficient in focusing the need for surgery and do no more than increase or decrease the suspicion of malignancy.

A few thyroid carcinomas can be diagnosed on examination of a hard irregular mass fixed to surrounding structures with associated lymphadenopathy. Laboratory investigations have a limited role: most patients are euthyroid, and although the presence of circulating thyroid antibodies may suggest thyroiditis, coexisting carcinoma cannot be excluded. Apart from a raised serum calcitonin level in medullary tumours, no specific markers for thyroid cancer have yet been identified. Screening programmes using thyroglobulin levels have failed to select patients with malignancy, although they may be useful in the detection of metastases or postoperative recurrence[6].

Scintigraphy can differentiate 'hot' (functioning) nodules which are generally benign[7] from 'cold' (non-functioning) nodules, which are malignant in around 16 per cent of cases[5]. Although ultrasonography can reliably delineate cystic lesions, 7 per cent of cysts may harbour a malignant tumour[8]. In addition to their expense, these 'shadow-producing' tests of an already palpable tumour are a fallible guide to pre-operative diagnosis.

Fine needle aspiration biopsy (FNAB) with cytological interpretation of the aspirated material offers a rational basis for planning operation on the basis of an accurate tissue diagnosis. Originally documented by the Scandinavians[9–12], the diagnostic value of the technique has since received enthusiastic support in several other countries[13–18]. There remains, however, a general disinclination in the UK to FNAB of the thyroid; it has been suggested that 'it should play no part in the investigation of thyroid disease'[19]. Our data from 562 patients would support its routine use in the pre-operative investigation of thyroid nodules.

Patients and methods

Patient selection

Between 1970 and 1985, FNAB was performed on 562 patients with nodular disease of the thyroid gland. There were 448 women and 114 men with a mean age of 48 years (range 17–77 years). The clinical diagnosis was either a solitary nodule within the thyroid or else a dominant nodule in a non-toxic goitre.

Before FNAB the patients were assessed according to their history and physical signs, serum thyroxine levels and autoimmune profile and also by radioisotope scintigraphy (^{131}I or [^{99m}Tc] pertechnetate). Ultrasonography was employed during the latter 3 years of the review. There were 369 patients (65·7 per cent) submitted to operation, 359 undergoing either partial or total thyroidectomy. The indications were because malignancy could not be excluded or to relieve symptomatic benign disease. In each case the histological diagnosis of the resected gland was compared with the pre-operative cytological diagnosis. A further four patients presented with inoperable tumours and the cytological diagnosis was confirmed at autopsy. A group of 189 asymptomatic patients did not undergo operation since clinical assessment and investigation had detected no evidence of neoplasia. All but 16 of these patients have been observed regularly in the outpatients clinic for at least 18 months for any changes suggestive of developing malignancy. They have remained well; repeat FNAB and other investigations have been performed as necessary.

A benign cytopathological diagnosis was considered a useful adjunct to the clinical diagnosis but was never the sole or principal reason for avoiding surgery.

Needle aspiration technique

FNAB is performed with the patient lying semi-supine and the neck extended. The thyroid nodule is immobilized with the fingers and thumb of one hand and the overlying skin cleaned with a spirit-based antiseptic. A 21 gauge 'green' needle (40 × 0·8 mm) attached to a 20 ml plastic disposable syringe is then inserted into the nodule varying the direction of insertion as required. Suction is applied by withdrawing the plunger

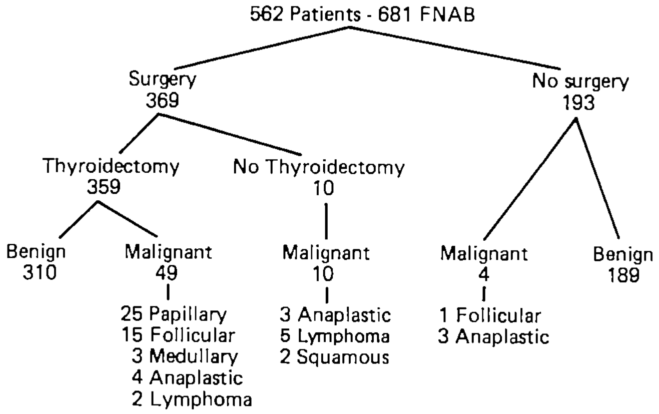

Figure 1 *Management and diagnosis of 562 patients with nodular thyroid disease*

of the syringe, and maintained using the extended thumb. This simple 'braced thumb' technique creates a negative volume pressure of 10–12 ml. Constant suction can also be effected using a syringe pistol[11]. The needle is advanced and withdrawn within the nodule three or four times at various angles, and the suction is then gently released. If cystic material is obtained readily, it is completely evacuated, smears made for cytological examination and re-aspiration performed. The needle is withdrawn and pressure is exerted over the biopsy site with a cotton wool 'ball' for about 5 min. For a large goitre it is prudent to aspirate more than one site.

Processing the specimen

The needle is separated from the syringe and re-attached after the syringe is filled with 2–3 ml of air. The contents of the needle lumen and syringe are blown on to clean, dry microscope slides. The aspirate is lightly spread over the slide with the needle point and air dried. The slides are labelled, fixed in methanol for 5 min and stained with a Romanovsky stain such as Giemsa or May–Grünwald Giemsa.

Cytological interpretation

The vast majority of FNAB were carried out and reported by the same person (A.J.W.). The cytopathological diagnoses were classified as follows:

(1) An inadequate biopsy where insufficient material was obtained for cytological assessment. Repeat aspiration was performed.

(2) Cytology was considered benign, when the aspirate showed natural thyroid epithelial cells with uniform nuclear size, shape and chromatin pattern. Scanty thyroid macrophages with a variable amount of blood or colloid were included as benign.

(3) An atypical diagnosis where the cells lay beyond the normal range, either in number or the degree of anisonucleosis.

(4) A follicular adenoma was often characterized by a uniform microfollicular pattern. The cells are evenly distributed and have small round nuclei with a distinct nuclear membrane and normal cytoplasmic staining.

(5) The aspirate was considered suspicious for malignancy either when there was abundant cellularity with dense 'clumping' of cells, or when some epithelial cells showed changes suggestive of malignancy (see 6). In these cases the aspiration was repeated.

(6) The cytological appearances were described as malignant when highly cellular smears showed unequivocal variation in size, shape and nuclear structure. Considering each malignancy in turn, the following morphological variants can be identified.

(a) In papillary carcinoma the cells are arranged in papillary sheets or monolayers and have a distinctive cytoplasm with sharply demarcated borders and variable-sized nuclei. Intranuclear cytoplasmic inclusions and psammoma bodies (extracellular concentric laminated concretions) are both helpful in the diagnosis.

(b) Follicular carcinomas are recognized by the frequent presence of follicular 'clusters' of cells much the same as in follicular adenomas. However, the nuclei are large and have a characteristically coarse, dense granular chromatin structure. The nuclear outlines are often indistinct or irregular and nuclear crowding or overlapping is frequently seen.

(c) Anaplastic carcinomas show a highly variable picture. Pleomorphic spindle-shaped or oval cells with bizarre nuclei are typically seen and mitotic figures and multinucleate giant cells are common.

(d) In medullary carcinoma the spindle-shaped, polygonal cells are usually well spread out. There is marked variation in nuclear size and the cytoplasm tends to include small dark granules. Background colloid is not seen but the presence of amyloid is diagnostic.

Clinical application

Operation was performed, where appropriate, in all cases of malignant cytology and also if the cytology was still suspicious after repeated FNAB. Follicular adenomas were all treated by lobectomy. Atypical cytological appearances were taken into account with other clinical features and lowered the threshold for surgical intervention. Although close follow-up of these cases with further FNAB was instigated, a high proportion came to operation. Benign cytology meant that operation was avoidable when this coincided with a clinical diagnosis of a benign lesion, and the absence of other pressing indications for intervention.

Results

Five hundred and sixty-two patients with nodular disease of the thyroid were assessed by FNAB (*Figure 1*); 119 patients (21 per cent)) had repeated aspiration because of unsatisfactory or inconclusive results from the first attempt, making a total of 681 biopsies. In two patients it proved impossible to obtain satisfactory material for cytological examination. Complications related to FNAB were not seen except for minimal haematomas which required no special measures.

Of the 369 patients treated surgically, 50 had a primary thyroid carcinoma confirmed by routine histopathological examination. There were 25 papillary, 15 follicular (including 3 Hurthle cell), 3 medullary and 7 anaplastic carcinomas. A further three patients had confirmation of an anaplastic carcinoma and one had follicular carcinoma demonstrated post mortem. Therefore, of 373 patients, 54 (14·5 per cent) had histopathological confirmation of a primary thyroid cancer. The details of their presentation and treatment are shown in *Tables 1* and *2*.

In 310 patients benign disease was confirmed by histopathological examination of the resected gland, and among this group there were 37 patients with a follicular adenoma.

In every case the histopathological diagnosis was made without knowledge of the cytological diagnosis.

The diagnosis of malignancy (Table 3)

Only 13 of the 54 patients (24 per cent) had a diagnosis of cancer suggested by physical examination. There was associated cervical lymphadenopathy in six cases of papillary carcinoma, and three patients each with follicular and anaplastic carcinoma presented a hard fixed mass palpable in the thyroid. Hoarseness was a distinctive clinical feature in two patients with anaplastic carcinoma.

Two female patients of the 54 were thyrotoxic, both for 18 months, and were controlled with carbimazole. One was found

Table 1 *Details of presentation of 54 patients with thyroid carcinoma*

	n	Average age (years)	Sex ratio (M:F)	Median duration of symptoms (months)
Papillary	25	39	1:1	12
Follicular	16	47	1:2	6
Medullary	3	35	1:2	5
Anaplastic	10	64	1:3	2

Table 2 *Details of treatment in 54 patients with thyroid carcinoma*

	n	Near-total thyroidectomy	Total lobectomy	Block dissection	External irradiation
Papillary	25	23	2	11	6
Follicular	16	14	1	1	8
Medullary	3	3	—	1	1
Anaplastic	10	4	—	—	9

Table 3 *The diagnosis of thyroid malignancy*

Modality	Objective	Correct (%)
Clinical	Malignancy	13/54 (24)
Isotope scintigraphy	Cold nodule	32/50 (64)
Ultrasound scan	Solid, solid-cystic lesion	17/22 (77)
FNAB	Malignancy	50/54 (93)

Table 4 *Diagnostic accuracy of fine-needle aspiration and cytology in 373 patients*

Histological diagnosis		Cytological diagnosis	
	n	Benign	Suspicious for or definitely malignant
Benign	310	308	2
Malignant	63	4	59

to have a mixed papillary and follicular tumour and the other a papillary carcinoma. Two patients had previously undergone subtotal thyroidectomy for nodular colloid goitre, 4 and 21 years earlier, and four others reported a goitre for at least 15 years. In five of these patients, follicular carcinoma, and in one anaplastic cancer, was confirmed by histopathology, supporting the view that nodular goitre is a possible predisposing risk factor for thyroid malignancy[20].

Fifty of the patients with confirmed thyroid carcinoma were investigated by radio-isotope scintigraphy. In 32 cases (64 per cent) this showed a 'cold' non-functioning nodule. The remainder showed normal diffuse uptake of the isotope. Twenty-two patients were also examined by ultrasonography and of these only seventeen were thought to have a discrete solid or solid-cystic lesion.

By contrast FNAB and cytology proved to be much better in the diagnosis of thyroid cancer with a total of 50 of the 54 primary thyroid carcinomas (92·6 per cent) correctly assigned by FNAB (*Table 3*).

Other malignancies were also detected within the thyroid. Metastatic squamous carcinoma diagnosed by FNAB was confirmed by direct laryngoscopy and biopsy in two patients, one patient having a primary tumour in the larynx, the other in the post-cricoid space. Another seven patients were found to have non-Hodgkin's lymphoma, confirmed in two following total thyroidectomy and in the others by lymph node biopsy. Thus FNAB and cytology provided an overall correct diagnosis for malignancy in 59 of 63 cases (93·7 per cent) (*Table 4*).

Carcinoma was overlooked in four patients with false benign cytology, an overall false negative rate of 6·3 per cent. In three of the four, histology showed follicular carcinoma (a 25 per cent false negative rate for follicular carcinoma) and in the fourth a papillary tumour (a 4 per cent false negative rate for papillary carcinoma). In two of the three follicular carcinomas fine-needle aspiration had diagnosed an adenoma, while the other two patients were thought to have benign goitres on cytological grounds. Both patients with presumed follicular adenoma underwent total lobectomy of the affected side and in one this was followed by subsequent near-total lobectomy on the other side once the diagnosis was made by histology. The second patient has been lost to follow-up. The two patients with presumed benign goitre also both came to operation. A woman who was found to have follicular carcinoma underwent bilateral subtotal thyroidectomy for a large unsightly goitre, while a 65-year-old man with a clinically malignant nodule underwent total thyroidectomy for a papillary carcinoma. Failure in the follicular lesions was due to the well differentiated nature of the tumours, a recognized problem[13], while in the other two cases it was probably due to inadequate sampling.

In 2 patients out of 310 with proven benign disease follicular carcinoma was incorrectly diagnosed by cytology, a false positive rate of 0·6 per cent. One of them was shown by histology to have an atypical nodular goitre and the other an atypical follicular adenoma. They both underwent near-total thyroidectomy and the case of the adenoma was the only occasion when an excessive resection was performed.

A total of 367 patients out of 373 received a correct cytopathological diagnosis with regard to malignancy. The sensitivity of the test for the detection of malignancy (the ratio of true positive cytology results to all patients with malignancy) is 93·7 per cent, and the specificity for benign conditions (the ratio of true negative cytology results to all patients without malignancy) is 99·4 per cent. The positive predictive value and the negative predictive value for FNAB are 96·7 per cent and 98·7 per cent respectively, and the overall accuracy rate (the fraction of test results that are correct) is 98·4 per cent.

In 52 of the 54 thyroid cancers (96 per cent) correctly diagnosed by FNAB, the morphological type of tumour was also accurately identified. Of the two incorrectly identified, in one a papillary tumour was diagnosed by cytology but subsequent histopathological examination showed this to be a follicular carcinoma. In the other a medullary tumour was thought to be a poorly differentiated papillary carcinoma on cytological examination.

Follicular adenomas

The diagnostic accuracy for FNAB in the identification of follicular adenomas is somewhat less than the overall figures. As already stated, one case of benign follicular adenoma was diagnosed by cytology to be a follicular carcinoma. In four other patients cytology had suggested nodular colloid goitre but histopathology confirmed the presence of follicular adenomas. Four patients with nodular goitre were diagnosed by cytology to have a benign follicular adenoma. The overall sensitivity for the identification of follicular neoplasms is 90·6 per cent while for follicular adenomas alone it is 86 per cent.

Discussion

The pre-operative identification of thyroid carcinoma on the basis of clinical findings, isotope scintigraphy and ultrasonography results in a low percentage yield of malignant disease[5,8,13,16]Nevertheless, there has been a striking lack of interest in the UK in reports that have shown the accuracy of cytology in differentiating benign from malignant thyroid swellings.

Fine needle aspiration biopsy is not new. In the latter half of the tenth century the famous Arabian physician Abulcasim described needle puncture of the thyroid to distinguish different types of goitre[21], but the technique was first used for the cytological diagnosis of a thyroid tumour in America in 1926[22]. In 1952 Soderstrom[9] described the use of FNAB in the diagnosis of a series of goitres, and since then it has become a routine and well-documented technique in all forms of thyroid disease[5,9-18].

The present study of 562 patients emphasizes the values of the procedure. Using FNAB a pre-operative diagnosis of malignancy was obtained in 92·6 per cent of patients with primary thyroid cancer, and 99·4 per cent of the lesions found to be benign by histopathological examination were correctly identified as such by FNAB and cytology. The overall accuracy rate for FNAB of 98·4 per cent is similar to the result reported by Lowhagen *et al.* in 1981[11].

However, there are limitations of the technique which need to be clearly recognized.

(1) Adequate material must be obtained for a diagnosis and this requires practice and attention to technical detail. In 443 of 562 patients (79 per cent) in the present study a cytological diagnosis was made on the first biopsy; only after a repeated aspiration was sufficient material for a cytological diagnosis

obtained in 560 patients (99·7 per cent). Furthermore, in the vast majority of cases the same person performed the biopsy and interpreted the cytology. This is an optimal situation not feasible in many clinics. Most aspiration biopsies will be performed by clinicians and the smears submitted to a laboratory, resulting in a lower diagnostic yield from fine-needle aspiration.

(2) False positive results are unusual and are reported to occur from 0 to 3·3 per cent[5,11]. In the present study the cytological results were considered as simply benign or malignant. The intermediate grading of 'suspicious for malignancy' necessitated repeat aspiration, but if the result was the same it was regarded as malignant since there is no reasonable alternative to operation in such cases. Although the false positive rate in this study was low (0·6 per cent), it is only by exploring patients with suspicious cytology that one can minimize the risk of missing a carcinoma.

(3) By contrast, a more serious problem for FNAB is the number of false negative results. If the diagnosis is based on cytology alone then malignant tumours can be missed. In this series, among 63 tumours there were 4 (6·3 per cent) false benign cytology results demonstrated by histology to be malignant. Provided that FNAB is considered as one part of the total diagnosis, to be seen in conjunction with other means of investigation, the number of false negatives will be minimized.

These failures are due in part to the inherent limitations of sampling, and to the recognized difficulty with follicular lesions. There is a widely held opinion that FNAB cannot differentiate benign from malignant follicular neoplasms[11], although some would disagree[23,24]. Recent studies involving planimetry also suggest that differences can be detected[25] and our results confirm this. The overall sensitivity for the identification of follicular neoplasms in this series was 90·6 per cent, while for follicular adenomas alone it was 86 per cent. Accepting therefore the limitations of FNAB, our results also highlight the problems with conventional means of investigating nodular thyroid disease. Malignancy was suspected on clinical grounds in only 13 of 54 patients with carcinoma. In the remaining 41, the lesions were clinically indistinguishable from benign nodules. It is impossible to estimate which of these patients would not have avoided surgery, or how long they would have been followed in the absence of FNAB.

Radio-isotope scanning is also limited in its application. Only two-thirds of patients with carcinoma had a distinct 'cold' nodule. The knowledge that carcinoma is very rare in hyperactive nodules is helpful, but against this, in two cases of toxic goitre, papillary carcinoma was correctly diagnosed by FNAB alone. Ultrasonography is also of only limited value. It is unable to detect fluid with the same accuracy as FNAB, and indeed the demonstration that a lesion is cystic does not prove it benign. Twenty-three per cent of the malignancies scanned in this series were not identified as discrete lesions.

By contrast FNAB and cytology can provide much useful information to help in the diagnosis and treatment of thyroid cancer.

(1) Fine-needle aspiration biopsy can reduce the number of patients with benign thyroid nodules submitted for diagnostic thyroid lobectomy without diminishing the discovery of malignancy[13,16]. Although malignancy was found in only 16·9 per cent of the patients submitted to surgery, most operations were performed for symptomatic benign disease, with a clear-cut pre-operative diagnosis. Carcinoma was confirmed in 96·7 per cent of those patients with a cytological diagnosis of malignancy. Without FNAB, an uncertain number of the 193 patients who avoided surgery would have been submitted to exploration of a 'cold' thyroid nodule to exclude malignancy.

(2) An appropriate degree of urgency can be assigned to malignant cases. It has been suggested that early removal of some differentiated cancers may reduce the possibility of later transformation to anaplastic carcinoma[26,27]. Depending on symptoms, benign nodular goitre can assume its place on the waiting list.

(3) Identification of the morphological type of the tumour by FNAB is helpful. The technique was accurate in distinguishing the tumour type in 57 of 59 patients with malignancy correctly diagnosed by cytology. Near-total thyroidectomy or occasionally lobectomy is the standard operation for differentiated carcinoma of the thyroid[28,29]. The pre-operative diagnosis enabled all such operations to be performed as one-stage procedures thus avoiding the complication rate associated with re-operation. Patients with anaplastic carcinomas and lymphomas are often best treated by radiotherapy and therefore with the help of cytology operation can be avoided in these cases. Similarly, a cytological diagnosis of squamous metastasis to the thyroid can prevent unnecessary operations.

(4) The pre-operative diagnosis can be considered with the patient and the possibility of total thyroidectomy and implantation of parathyroid glands fully explained.

(5) Fine-needle aspiration biopsy and cytological diagnosis has the important advantage of providing greater sensitivity, specificity and accuracy when compared with the less informative standard means of investigation, and at a lower cost and morbidity than a diagnostic thyroid lobectomy.

Objections to the use of FNAB in the diagnosis of thyroid disease are important and merit discussion. The danger of seeding cancer cells by needle biopsy has been offered as a serious contra-indication. There are only two reports of tumour dissemination of this type, both occurring with a large-bore cutting-needle biopsy of the thyroid[30,31]. Using a fine-needle aspiration there is no direct evidence of tumour dissemination or of an adverse effect on prognosis[32]. Although it is likely that tumour cells spread along the needle tracks, the clinical implications are minimal since most malignant tumours, the area of needling included, are subjected to subsequent surgical excision or radiotherapy. Experimental studies have shown that fine-needle aspiration of lymph nodes containing metastatic cancer does not increase the release of cancer cells into the efferent lymphatics in an animal model[33]. Finally, long-term follow-up of patients with breast cancer diagnosed by FNAB matched with non-aspirated controls showed no difference in survival after more than 20 years[34].

Despite its well documented success in identifying thyroid cancer, there is resistance to FNAB for reasons beyond these obvious objections. It has been suggested that this resistance stems from the subjective nature of the diagnosis, which is based on experience and the principles of cytodiagnosis, and not, so far, on the demonstration of absolute figures or images[35]. Essential to the success of FNAB is a competent cytologist who is prepared to give an opinion.

A common complaint from pathologists is their inability to interpret the aspirate. While interpretation is not always easy, an increasing number of studies suggest that it can be learnt. Although a consistent, definitive answer is not possible in every case, the information provided by cytology is certainly superior to that provided by conventional means of investigation. Exfoliative cytology for the diagnosis of cervical cancer took many years to become established; in fact 24 years elapsed between its introduction and gaining acceptance by the American Cancer Society[36]. Cervical smears are now screened in vast numbers. Perhaps it is a matter of time before FNAB of the thyroid becomes a routine service for the diagnosis of thyroid cancer, dominating other less accurate modes of investigation.

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Combination fine-needle aspiration cytology and intrarenal manometry at the onset of renal dysfunction

Twenty-three consecutive cadaveric renal allograft recipients immunosuppressed with cyclosporin have been monitored three times a week by fine-needle aspiration cytology and intrarenal manometry until discharge from hospital or until 30 days post-transplant. Standard criteria were used to determine the cause of allograft dysfunction. The onset of allograft rejection was marked by an elevation of the total corrected increment score by fine-needle aspiration cytology in 80 per cent of rejection episodes whereas intrarenal pressure was raised in only 46·6 per cent. However, intrarenal pressure was greater than 40 mmHg on a single occasion in 16 measurements performed on allografts showing evidence of cyclosporin nephrotoxicity. By combining fine-needle aspiration cytology and intrarenal manometry the sensitivity of these tests for allograft rejection was increased to 93·3 per cent at the onset of renal dysfunction. Our results demonstrate that fine-needle aspiration cytology is more sensitive than intrarenal manometry as a single investigation. However, the combined test may have an important role in the differentiation of allograft rejection and cyclosporin nephrotoxicity in the early management of renal allograft recipients.

Keywords: Cyclosporin, renal cadaveric transplantation, fine-needle aspiration cytology, intrarenal pressure

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The introduction of cyclosporin A (CyA) into clinical renal transplantation has significantly improved results[1]. However, there have been difficulties in some patients in distinguishing between the rejection and nephrotoxicity produced by the CyA. Two investigative techniques, fine-needle aspiration cytology (FNAC) and intrarenal manometry (IRM) have developed in recent years which attempt to assess early renal allograft dysfunction.

It was Pasternack[2] who initially suggested that FNAC may reflect the cellular infiltrate of renal allografts during rejection episodes and this technique has been quantified by Hayry and von Willebrand[3,4]. It is now a widely practised method of monitoring early allograft dysfunction.

Wagner *et al.*[5] first described the changes in subcapsular hydrostatic pressure as a means to differentiate graft rejection from CyA nephrotoxicity. The drawback of a subcapsular microcatheter was overcome by Salaman and Griffin[6] by measuring the intrarenal pressure with a 25 FG spinal needle. Both FNAC and IRM individually have shown favourable results in the differential diagnosis of allograft dysfunction so our study aims have been to compare these two procedures and also to determine whether the combination of these investigations can improve diagnosis at the onset of renal dysfunction.

Patients and methods

Twenty-three consecutive cadaveric renal allografts were monitored by FNAC and IRM three times a week starting 3–5 days post-transplant until discharge from hospital or until 30 days post-transplant. Oral CyA was started postoperatively at 15 mg kg^{-1} day^{-1} with planned reduction to 12·5 mg kg^{-1} day^{-1} at 2 weeks. Prednisolone was administered at 0·4 mg kg^{-1} day^{-1}.

Fine needle aspiration was performed as described by Hayry and von Willebrand[4]. After antiseptic skin preparation, a 25 FG spinal needle is introduced into the upper pole of the renal transplant and attached to a dry plastic syringe. Then 10–20 μl of fluid containing intrarenal cells are withdrawn into the syringe and immediately resuspended in 2 ml of RPMI 1640 medium containing 5 per cent human serum albumin and heparin. Cytocentrifuge preparations are mounted on glass slides, fixed and stained with May–Grunwald–Giemsa stain.

A sample of peripheral blood was treated in an identical manner. The true cellular graft infiltrate was calculated by subtracting the peripheral blood differential white cell count from the aspirate differential white cell count. The resultant count is scored as suggested by Hayry and von Willebrand[3] to derive a total corrected increment (TCI). All preparations were reported by a single observer without knowledge of clinical details.

To measure intrarenal pressure (IRP), a 25 FG spinal needle primed with saline is inserted into the upper pole of the transplant as for FNAC. The needle is connected by manometry tubing primed with saline and a small air bubble to a SiPro kidney manometer[6]. The manometer pressure is increased to cause movement of the air bubble towards the kidney after which the pressure is decreased to stop movement of the air bubble. The manometer pressure at which the air bubble stops is considered to represent intrarenal pressure. Duplicate recordings are made and the mean pressure calculated. Peripheral blood pressure is recorded at the end of the procedure.

FNAC scores and IRP recordings were retrospectively assigned to one of four states determined by clinical assessment of patients, serum biochemistry, RIA plasma CyA levels (routinely measured twice a week), response to antirejection therapy and response to a reduction in CyA dosage. A response was regarded as clinical and biochemical improvement to the pre-episode levels. Ultrasonography, isotope scintigraphy and contrast radiology were performed to exclude technical problems as clinically indicated during episodes of renal dysfunction. Open biopsy was performed in five grafts in which there was doubt concerning graft status. Patients were considered to have (a) stable or improving renal function or (b) rejection or (c) cyclosporin nephrotoxicity or (d) acute tubular necrosis (ATN). Data were excluded if graft status could not be clearly assigned to one of these states. In addition, only the FNAC and IRP recordings during the first three days of a rejection episode are presented.

The Mann–Whitney *U* test with correction for large numbers was used for statistical analysis.

Table 1 *Fine-needle aspiration cytology (TCI score) and intrarenal pressure measurements (mmHg) related to graft status*

Graft status	Stable ($n=23$)	Rejection ($n=10$)	Nephrotoxic ($n=7$)	Acute tubular necrosis ($n=5$)
TCI				
Observations	68	34	16	10
Mean ± s.d.	0·98 ± 0·9	2·69 ± 1·13	1·17 ± 1·7	1·46 ± 1·1
Median	0·7	2·75 *$P<0·001$	1·0 *$P<0·02$ **$P<0·002$	1·07 *$P<0·05$ **$P<0·005$
IRP (mmHg)				
Measurements	76	40	16	13
Mean ± s.d.	23·4 ± 13·4	31·5 ± 14·5	24·8 ± 9·1	35·5 ± 22·2
Median	20	27·5 *$P<0·002$	25 *n.s. **n.s.	30 *$P<0·05$ **n.s.

Significance of difference to *stable function and **rejection

Table 2 *RIA plasma cyclosporin levels (ng/ml)*

Graft status	Estimations	Mean ± s.d.	Median (interquartile range)
Stable	63	280·7 ± 223·7	210 (110–365)
Rejection	27	309·2 ± 229	285 (130–447·5)
Nephrotic	17	679 ± 277	700 (450–1000)*
ATN	5	219·8 ± 127·3	200 (180–205)

Levels <62·5 and >1000 considered as 62·5 and 1000 respectively
*$P<0·001$

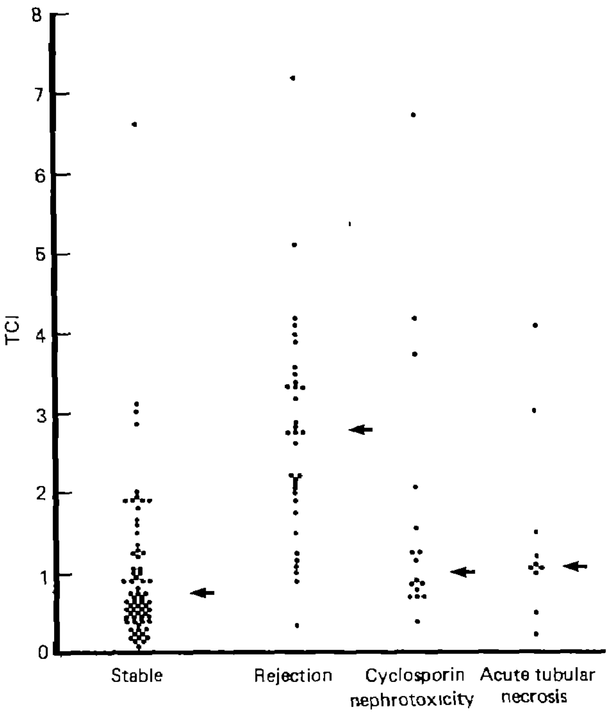

Figure 1 *Fine-needle aspiration cytology TCI scores over the first 30 days after transplantation (←median)*

Results

Of the 23 patients, 5 showed failure of primary function requiring postoperative dialysis but ultimately functioned well enough to permit withdrawal of renal support. Seven patients had evidence of CyA nephrotoxicity and ten experienced rejection episodes (*Table 1*). The CyA levels during stable function were not significantly different from those during rejection and ATN (*Table 2*). However, levels were significantly higher during nephrotoxicity ($P<0·001$). All seven nephrotoxic episodes showed improvement in renal function after reduction in CyA dosage with increased urine output and return of serum biochemistry to pre-episode levels. All 15 rejection episodes responded to pulsed methylprednisolone therapy and at a mean follow-up of 6 months, no graft loss in this group had occurred. However, one patient with a functioning graft died at 2 months post-transplant from cytomegalovirus infection.

A single episode of macroscopic haematuria was experienced by one patient shortly after FNAC and IRM. No other complications were encountered in this study.

Fine-needle aspiration cytology

A total of 164 aspirations were performed. However, 20 preparations were considered to be unrepresentative as they contained less than 7 per cent tubular cells[7]. It was also decided not to present data from patients after the third day of their rejection episode since all showed the effect of methylprednisolone administration. Similarly, six examinations in two patients with obstructed ureter are excluded from this study. These exclusions leave a total of 128 preparations which were then analysed with respect to the four renal states (*Table 1*). Of 23 patients monitored during stable renal function 13 showed no episodes of rejection in the first 30 days after transplantation. In these patients the TCI ranged from 0·2 to 1·9 with a mean of 0·71 ± 0·48 s.d. Taking a 99 per cent tolerance limit gave an upper limit of 2·04; therefore, it seemed logical in our group of patients to adopt a TCI > 2·0 to indicate immunoactivation in the graft. On examination of the results obtained on the first day of the rejection episodes, 12 of the 15 preparations had a TCI score > 2·0.

Four other patients in this study with clinically stable renal function had TCI scores > 2·0 but all four aspirates were made 48 h before a clinically evident rejection episode (*Figure 1*). The two elevated scores in patients with ATN were present before rejection episodes confirmed by graft biopsy. Three patients with nephrotoxicity, as judged by the response to dosage reduction, had TCI scored > 2·0. However, in two patients it is clear that the aspirates immediately preceded rejection episodes and in the third, the aspirate reflected an incompletely treated rejection.

Intrarenal manometry

One hundred and forty-five intrarenal pressure (IRP)

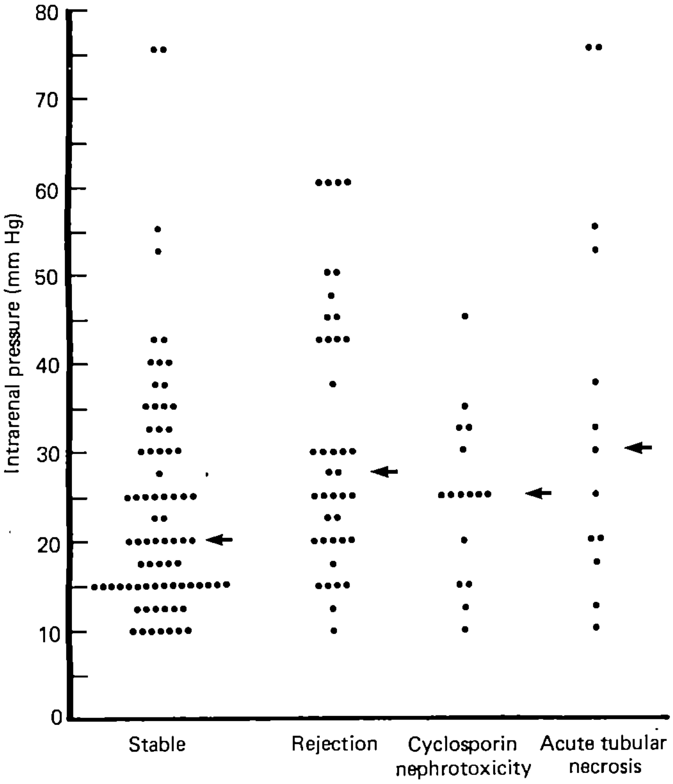

Figure 2 *Intrarenal pressure (mmHg) over the first 30 days after transplantation (←median)*

measurements were available for analysis after exclusions were made as for FNAC (*Table 1*). On seven occasions there was a technical failure to record IRP. Duplicate IRP measurements showed a high correlation ($r = 0.93$). There was no correlation of IRP to systolic or diastolic peripheral blood pressure. The IRP of the 13 grafts showing no rejection episodes ranged from 10 to 75 mmHg with a mean of 20.9 ± 12.5 s.d. Only two measurements were greater than 35 mmHg, so we accepted Salaman's reported upper limit of normal IRP as 40 mmHg[6]. Examining the data for all IRP measurements obtained with respect to the four renal states, it was found that there is a highly significant difference in the IRP with stable function compared with measurements during the first 3 days of a rejection episode ($P < 0.002$). No significant difference was noted between rejection and CyA nephrotoxicity ($P = 0.109$) (*Figure 2*).

Re-examining the data using 40 mmHg as the discriminating IRP, it was found that six measurements in two patients were greater than 40 mmHg despite apparently stable renal function. Conversely, 13 of 40 IRP measurements performed during rejection were greater than 40 mmHg. Furthermore, using measurements performed on the first day of renal dysfunction ultimately diagnosed as rejection only seven of the fifteen rejection episodes were associated with an abnormally high IRP.

Only one of sixteen measurements performed on grafts with nephrotoxicity was associated with an IRP > 40 mmHg; however, four of thirteen IRP measurements were raised in grafts with ATN.

Combination FNAC and IRM

In *Figure 3*, TCI values and intrarenal pressures are correlated for renal dysfunction episodes. Using the discriminant values of TCI > 2·0 and IRP > 40 mmHg, derived from investigations on the first day of renal dysfunction, it can be seen that 14 of the 15 rejections were identified. This gives a sensitivity for the combined investigation of 93·3 per cent, though studies in patients with nephrotoxicity revealed that five of sixteen measurements were also positive for rejection and thus the specificity (i.e. true negative) was only 68·8 per cent. However, it was considered that four of the false positive results in three nephrotoxic patients were the result of an elevated TCI in association with rejection episodes (see above).

Discussion

FNAC is now a widely practised technique to investigate renal allograft dysfunction. The total corrected increment was devised to quantify the severity of rejection episodes. The 'Transplant aspiration cytology: quantity control analysis in 1984' by Hayry[8] demonstrated that the criteria for reporting a set of preparations was very consistent between 30 centres participating in the study. However, it is recognized that different patterns of cellular infiltrate are observed with different immunosuppressive regimens in patients without clinical evidence of rejection[9]. This demands that each centre must establish its own TCI range for patients with stable renal function, so we have derived our upper limit by considering only those patients who demonstrated no evidence of rejection in the first 30 days post-transplant. In our experience this is a good discriminating level as 12 of 15 rejection episodes were identified at the onset of renal dysfunction (sensitivity 80 per cent). We support the view that FNAC may play an important role in detection of rejection in patients with primary failure of function after transplantation[10]. In this study, two patients with ATN were shown to have rejection on renal biopsy. Both patients had elevated TCI score before the biopsy and, in retrospect, it is clear that FNAC predicted rejection earlier than the renal biopsy. No severe rejection episodes occurred in this study group of patients as reflected by the relatively low TCI scores overall during rejection and the response of all patients to pulsed methylprednisolone without loss of any grafts.

Wagner *et al.*[5] elegantly demonstrated an increase in subcapsular hydrostatic pressure during rejection within 4 weeks of transplantation. Salaman and Griffin simplified the procedure by measuring the resistance to dispersion of saline within the kidney through a spinal needle. This pressure may reflect the interstitial pressure and may be expected to rise during the first few days of rejection episodes. Although all of our IRP measurements were obtained during the first 30 days

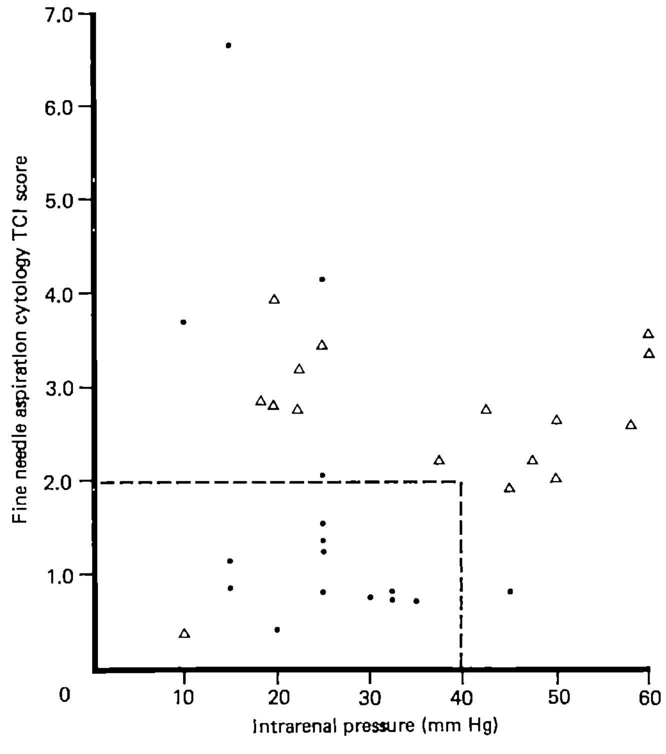

Figure 3 *Combined FNAC and IRM for renal dysfunction episodes. Δ First day of rejection episode; ● cyclosporin nephrotoxicity*

post-transplant, the results for stable renal function, nephrotoxicity and ATN are comparable to those reported in the Cardiff study[6]. However, during the first 3 days of the rejection episodes only 32·5 per cent of our measurements were >40 mmHg, whereas the Cardiff study reported two-thirds of rejection episodes showing elevation of IRP just before or at the time of the first rise in serum creatinine[11]. We primed the spinal needle with saline before the introduction into the kidney and this may account for minor differences in IRP measurements. On six occasions blood was noted in the hub of the spinal needle at the end of the IRP measurement so these were excluded from the study. We have presumptive evidence that we failed to enter the kidney in one patient : the FNAC performed before IRM contained no parenchymal cells so the IRP was excluded from the study.

This study has demonstrated that as a single investigation FNAC is more accurate than IRM in the diagnosis of graft rejection at its onset. Although during CyA nephrotoxicity the IRP was unlikely to be greater than 40 mmHg, we have found IRM alone to be an unhelpful investigation at the onset of renal dysfunction. However, IRM combined with FNAC improved the sensitivity for graft rejection and so the combined investigation may prove to be one of diagnostic value in the management of renal allograft recipients in the first 30 days after transplant.

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Blood viscosity in patients with bone fractures and long term bed-rest

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Eighteen patients with bone fractures and without systemic disease were studied for blood rheology. Blood and plasma viscosities, haematocrit, red cell aggregation and filterability as well as plasma colloid oncotic pressure were measured. Results show that patients exhibit a substantial haemorheological deficit on admission. During bedrest this returns to normal, owing to marked 'autohaemodilution'. It is concluded that trauma causes increased viscosity of blood in these patients. This change could predispose to deep vein thrombosis. However, such a risk is reduced by 'autohaemodilution' which is most probably an effect of immobilization.

Keywords: Haemorheology, bed-rest, haemodilution, deep vein thrombosis

The viscosity of blood is determined by a number of factors of which haematocrit, plasma viscosity, red cell deformability and red cell aggregation seem to be most decisive. There have been reports on increased viscosity of blood due to surgical trauma[1]. Blood viscosity and related variables have also been correlated to the incidence of deep vein thrombosis (DVT)[2]. DVT is one of the most frequent and threatening complications encountered whenever prolonged bed-rest is necessary. At present no data are available concerning either the haemorheological effects of bone fractures or those of prolonged immobilization.

Patients and methods

Six men and eleven women (average age 63 ± 24 years) were examined. The reasons for hospitalization were fractures of the spine ($n = 14$), the pelvis ($n = 2$) and the femur ($n = 1$). Patients had been confined to bed for at least 30 days and were without systemic illness (criteria: physical examination and routine blood tests). Heparinization with calcium heparin (3 x 5000 units/day) was a routine measure. Otherwise medical treatment was symptomatic. Blood rheology was tested on admission, 15 and 30 days after the start of the immobilization. The control group consisted of 17 apparently healthy individuals (criteria as above) matched for age and sex.

After an overnight fast a 19 G needle was inserted into an antecubital vein, venous occlusion was released and 20 ml of blood was drawn into a preheparinized syringe (final concentration 12·5 units/ml) with minimal suction. This technique was shown to avoid possible sampling artefacts due to posture or occlusion time[3].

The variables tested were: blood viscosity at 3 shear rates using the LS 30 (Contraves)[4] at both native and standardized (45 per cent) haematocrits at 37°C, plasma viscosity in a capillary viscometer[5], blood cell filterability by Nuclepore (5 μm pores) filtration[6], red cell aggregation using an automated transparent cone and plate viscometer[7], colloid oncotic pressure by the semi-permeable membrane technique[8].

Statistical analysis was performed by Student's *t* test when data were distributed normally, otherwise by the multiple comparison method of Wilcoxon and Wilcox for paired data[9]. The null hypothesis was rejected when $P < 0{\cdot}05$.

Results

At entry patients have higher blood and plasma viscosities than controls (*Table 1*). There is no significant intra-individual change of any parameter after 15 days bed-rest. After 30 days, however, a significant fall in haematocrit and in native blood viscosities at all shear rates can be detected. Plasma viscosity tends to decrease and blood cell filterability to increase, which does not reach statistical significance. All other parameters remain constant during bed-rest. The cross-sectional comparison of patients after 30 days' immobilization with controls shows that in patients the haematocrit standardized blood viscosities are still higher while the haematocrit is lower than in controls.

Discussion

The present results indicate that bone fractures are associated with haemorheological deficits similar to those observed in surgical trauma[1]. There is a significant increase in the viscosity of the patient's blood and plasma on admission compared with an age and sex matched control group. This is not due to haemoconcentration or an increase in red cell rigidity. A possible reason is a rise in plasma fibrinogen, which would strongly influence blood and plasma viscosities. However, red cell aggregation (also fibrinogen-dependent) is not elevated, which indicates that other factors might contribute. Possibly the different rheological properties of fibrinogen and early and late derivatives of fibrinogen might explain these findings[10].

During strict immobilization a significant 'autohaemodilution' occurs. The underlying mechanism might be an expansion of plasma volume, which would explain the fall in haematocrit-dependent parameters as well as the (non-significant) decrease in plasma viscosity. The cause is unclear, but it seems likely that it reflects the complex adaptation of the cardiovascular system to bedrest. Possibly a decrease in sympathetic tone could be involved. Adrenaline changes blood fluidity *in vitro*[11], and high sympathetic tone like in stress is associated with decreased fluidity[12]. Theoretically, low dose heparin might also be considered to play a causative role. A modification of haemorheological variables after heparinization has been reported[13,14]. However, it leads to a haematocrit-independent decrease of low shear blood viscosity[14], rather than haemodilution. Recovery from the acute phase reaction in connection with bone fracture may also influence the intra-individual changes. This should influence foremost inflammation sensitive parameters (low shear viscosity, plasma viscosity, red cell aggregation) and not haemodilution. However, stress and trauma-related blood volume contraction at base line cannot be ruled out entirely.

Surgical patients who later suffered from postoperative DVT show increased blood viscosity[15]. Similarly post-thrombotic syndrome is associated with a significant haemorheological deficit[16]. In addition, there is circumstantial evidence relating DVT and rheology factors[2]. This poses the obvious question of whether immobilization is a risk factor for DVT through haemorheological mechanisms. The present data rejects this hypothesis. In fact blood viscosity does decrease through haemodilution and not increase, which (if one accepts the above argument) should prevent rather than induce DVT, as shown in a clinical trial[17]. No patient in this trial developed clinical DVT.

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Table 1 *Haemorheological data during prolonged bed rest*

Parameter	Controls	Patients		
		Baseline	After 15 days	After 30 days
BV, D=0·7 s^{-1} (mPa s)	22·4±8·2‡	38·4±20·9	34·5±16·7	22·8±10·8*†
BV, D=2·4 s^{-1} (mPa s)	13·5±5·3‡	19·6±10·0	20·9±13·0	12·4±5·6*†
BV, D=94·5 s^{-1} (mPa s)	4·4±0·7‡	5·3±1·61	5·0±1·28	4·2±10·0*
BV$_{45}$, D=0·7 s^{-1} (mPa s)	22·3±8·1‡	37·5±17·5	35·0±9·7	39·4±17·8§
BV$_{45}$, D=2·4 s^{-1} (mPa s)	13·4±5·4‡	18·7±6·9	17·4±2·8	18·2±4·7§
BV$_{45}$, D=94·5 s^{-1} (mPa s)	4·4±0·7‡	5·2±0·8	5·1±0·5	5·4±0·8§
PV (mPa s)	1·20±0·06‡	1·26±0·10	1·28±0·11	1·23±0·10†
BCF (units)	0·66±0·12	0·60±0·19	0·54±0·17	0·65±0·18
RCA (units)	12·8±3·8	10·2±4·8	8·6±4·2	10·6±2·4
Haematocrit (%)	45·1±5·3	45·3±8·0	43·8±10·5	38·2±9·7*†§
COP (mmHg)	28·2±1·8	28·6±1·9	28·5±1·9	28·3±2·3

*=significant difference to base line
†=significant difference to 15 days value
‡=significant difference between controls and patients at base line
§=significant difference between controls and patients after 30 days
BV, blood viscosity; D, shear rate; BV$_{45}$, blood viscosity at haematocrit of 45 per cent; PV, plasma viscosity; BCF, blood cell filterability; RCA, red cell aggregation; COP, colloid oncotic pressure

Our laboratory[18] and others[19,20] have shown that regular physical activity leads to an amelioration of blood rheology. Therefore one could speculate that lack of physical activity, an accepted cardiovascular risk factor, might induce a worsening of blood fluidity. The present results neither support nor reject this hypothesis, as 30 days of immobilization is too short a period to give an answer to this particular question.

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Effect of topical and systemic antibiotics on bacterial growth kinesis in generalized peritonitis in man

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Quantitative bacteriology in peritoneal exudate was studied in 40 patients with generalized peritonitis of small intestinal, appendicular or colonic origin. Bacterial growth kinesis was measured in 28 of the patients. Systemic antibiotics given before operation resulted in a significant reduction in both the concentration and growth rate of viable bacteria in the peritoneal fluid. Lavage of the peritoneal cavity with saline resulted in a further reduction in growth rate in patients given pre-operative systemic antibiotics by an effect attributable to simple dilution. In contrast, peritoneal lavage with tetracycline (1 mg/ml) resulted in complete inhibition of bacterial growth in the residual peritoneal fluid. These observations support the policy of giving systemic antibiotics to patients with generalized peritonitis as soon as the diagnosis has been made and provide bacteriological evidence for the value of peroperative antibiotic peritoneal lavage.

Keywords: Antibiotics, peritoneum

Intraperitoneal and wound infection are common complications of operations for peritonitis[1–3] and the risk of sepsis is related to the degree of operative contamination. If the initial treatment of peritonitis is suboptimal and peritoneal sepsis becomes established, antibiotics given postoperatively may fail to influence the outcome. Excellent results in terms of prevention of septic complications in both elective and emergency abdominal surgery have been reported with the use of tetracycline lavage of the wound and peritoneal cavity[4]. As a result, we understand that tetracycline lavage has become common practice in Scotland. Yet antibiotic peritoneal lavage is still largely discredited or frowned upon world-wide[5]. The lack of a prospective controlled trial in patients with severe generalized peritonitis possibly underlies widespread scepticism on the value of tetracycline lavage especially outside the UK. The problems inherent in such a trial including, in our case, ethical considerations are considerable. As an alternative we have measured the effect of systemic antibiotics, saline lavage and tetracycline lavage on the number of micro-organisms and on their growth rate in generalized peritonitis in man.

Patients and methods

Patients

Forty patients with peritonitis of small intestinal, appendicular or colonic origin of <48 h duration were studied. All were confirmed to have generalized peritonitis affecting both the supra- and infracolic compartments at laparotomy performed through a vertical midline incision. Patients with a gastric or duodenal source or in whom an abscess or localized peritonitis was found were excluded. The distribution of the patients according to the source of the peritonitis is shown in *Table 1*.

Antibiotics

In 23 patients systemic antibiotics were given after the diagnosis had been confirmed at laparotomy and bacteriological specimens taken. In 17 patients, because of clinical concern about delay in instituting treatment, intravenous metronidazole (500 mg) and cefotaxime (2 g) were given pre-operatively. The decision for or against pre-operative antibiotics was made by the surgeon in charge of the patient and was influenced by the apparent severity of peritoneal contamination according to clinical signs. The distribution of patients given antibiotics before operation is also shown in *Table 1*.

Bacteriology

Quantitative bacteriological counts. On opening the peritoneal cavity sterile universal containers were filled to capacity with a representative sample of peritoneal fluid. Similar samples were taken after each lavage and transported immediately to the bacteriology laboratory for serial dilutions and culture. A Gram stain was made of a smear of the initial sample of peritoneal fluid and gave an approximate guide to the potential variety and concentration of organisms. Bacterial colony counts were made in all 40 patients using a conventional surface colony counting technique. Serial dilutions of the sample were made and aliquots inoculated on to plates of blood, MacConkey and Sabouraud agar for aerobic organisms and prereduced blood and gentamicin–blood agar for anaerobes. The aerobic plates were incubated at 37°C for 18–24 h and the anaerobic plates for 48 h at 37°C in an anaerobic cabinet (Don Whitley Scientific Ltd., Shipley, UK). An aliquot was also inoculated into Robertson's meat broth.

Bacterial growth kinetics. Bacterial growth in the peritoneal fluid of 28 patients was measured electronically using a Malthus microbiological growth analyser (Malthus Instruments, Stoke-on-Trent, UK) by monitoring the change in conductance in the culture medium which is directly proportional to the number of viable bacteria[6]. The selection of the 28 patients for study of bacterial growth kinetics was simply on the basis of the availability of the Malthus instrument.

Lavage technique. After the first sample of fluid was taken the peritoneal cavity was aspirated as completely as possible and any potential source of continuing contamination closed. Patients were then randomly allocated according to the last digit of their unit number to lavage of the peritoneal cavity with two 500 ml aliquots of physiological saline or tetracycline in saline (1 mg/ml) and samples of the residual peritoneal fluid were taken. In six patients allocated to tetracycline lavage a further sample of residual peritoneal fluid was taken after 1 h.

Table 1 *Distribution of patients according to source of peritonitis and pre-operative antibiotic administration*

Site	Number	Pre-operative antibiotics
Small bowel	9	4
Appendix	13	3
Colon	18	10
Total	40	17

Results

The number of species isolated according to the source is shown in *Figure 1*, the distribution of species in *Table 2* and the concentration of organisms in the peritoneal fluid in *Figure 2*. *Escherichia coli* and *Streptococcus faecalis* were the commonest aerobic organisms and *Bacteroides fragilis* was the commonest anaerobe (*Table 2*).

There was a wide variation in the concentration of viable organisms in the peritoneal fluid but there was a significant difference between the effect of pre-operative and no pre-operative systemic antibiotics, (median $3{\cdot}2 \times 10^4$ CFU/ml *versus* $2{\cdot}5 \times 10^7$ CFU/ml; $P<0{\cdot}01$, Wilcoxon rank sum test).

The mean growth curve in the first sample of peritoneal fluid before lavage in 14 patients not given pre-operative antibiotics is shown in *Figure 3* and is typical of a polymicrobial inoculum. The rate of growth in the first sample in 14 patients given pre-operative antibiotics was slower and this difference was significant throughout the incubation period ($P<0{\cdot}01$ Wilcoxon test, *Figure 3*).

The effect of saline lavage on the growth of bacteria in the residual peritoneal fluid in 14 patients (9 of whom had received pre-operative antibiotics) is shown in *Figure 4*. The rate of detection of growth was significantly reduced in lavage patients throughout the incubation period regardless of whether antibiotics had been given pre-operatively, except after 8 h incubation in the group not receiving antibiotics. The delay in detection of growth is similar to the effect observed during serial *in vitro* dilutions of a bacterial inoculum and is entirely explicable on this basis.

In contrast, after tetracycline lavage in 14 patients (5 of whom had received pre-operative antibiotics), there was complete inhibition of bacterial growth in the residual peritoneal fluid regardless of whether pre-operative antibiotics had been given (*Figure 5*). This effect was still present in a further sample of fluid taken 1 h after tetracycline lavage in six cases (*Figure 6*).

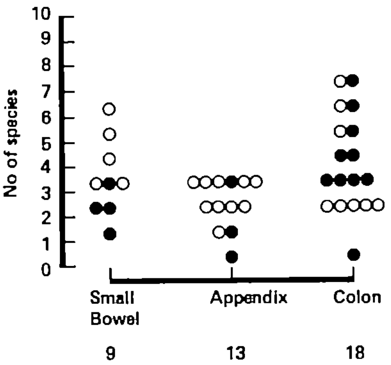

Figure 1 *Number of species of micro-organisms isolated from peritoneal fluid according to the source of peritonitis in 40 patients:* ○, *no pre-operative antibiotics (23 patients);* ●, *pre-operative antibiotics (17 patients)*

Discussion

This study was conducted during the routine clinical management of patients with generalized peritonitis of small

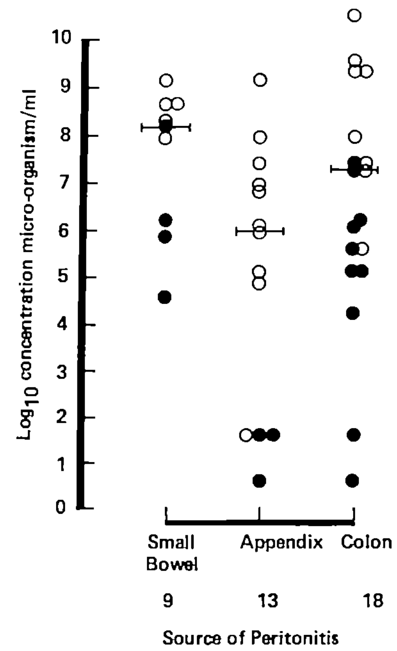

Figure 2 *Concentration of micro-organisms in peritoneal fluid according to the source of peritonitis in 40 patients:* ○, *no pre-operative antibiotics (23 patients);* ●, *pre-operative antibiotics (17 patients);* ⊢—⊣ *represents median*

Table 2 *Distribution of types of micro-organisms according to the source of peritonitis*

	Small bowel ($n=9$)	Appendix ($n=13$)	Colon ($n=18$)	Total ($n=40$)	Percentage of total organisms
Aerobes					
Streptococci	6 (33)	2 (13)	10 (24)	18 (24)	15
Enterococci	2 (11)	2 (13)	9 (21)	13 (17)	11
Staphylococci	—	2 (13)	1 (2)	3 (4)	2
Enterobacteria	9 (50)	12 (75)	31 (74)	52 (68)	43
E. coli	8 (44)	10 (63)	19 (45)	37 (49)	31
Klebsiella sp.	1 (6)	1 (6)	5 (12)	7 (9)	6
Proteus sp.	—	1 (6)	5 (12)	6 (8)	5
Pseudomonas sp.	—	—	2 (5)	2 (3)	2
Fungi	3 (17)	—	—	3 (4)	2
Total aerobes	18 (100)	16 (100)	42 (100)	76 (100)	63
Anaerobes					
Bacteroides	5 (50)	9 (75)	15 (65)	29 (64)	24
Bacteroides fragilis	5 (50)	9 (75)	13 (58)	27 (60)	22
Clostridia	4 (40)	—	6 (26)	10 (22)	8
Streptococci	1 (10)	—	1 (4)	2 (4)	2
Microaerophilic streptococci	—	3 (25)	1 (4)	4 (9)	3
Total anaerobes	10 (100)	12 (100)	23 (100)	45 (100)	37
Total	28	28	55	121	

Figures in parentheses are percentages

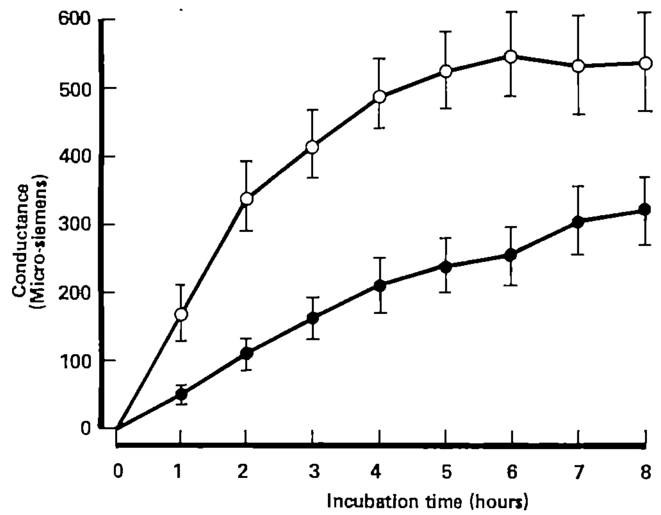

Figure 3 *The effect of pre-operative systemic antibiotics on bacterial growth in the initial sample of peritoneal fluid in 28 patients: ○, no pre-operative antibiotics (14 patients); ●, pre-operative antibiotics (14 patients); bar represents ±1 s.e.m.*

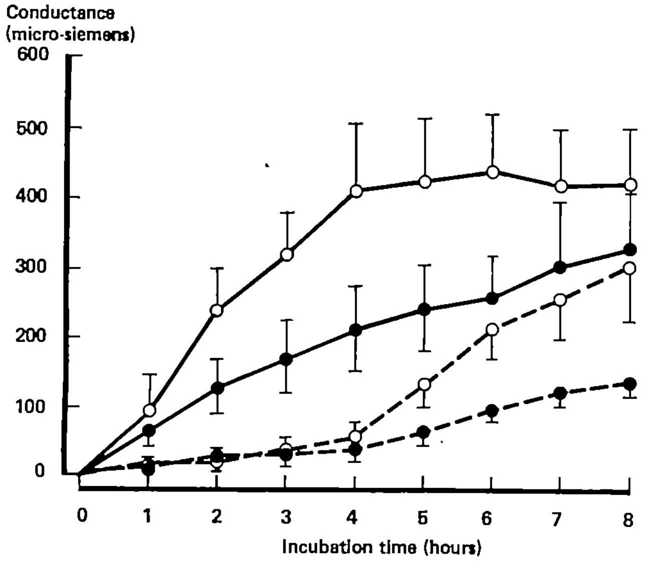

Figure 4 *The effect of saline lavage on bacterial growth in 14 patients: ○——○, no pre-operative antibiotics (5 patients); ○– – –○, no pre-operative antibiotics after two lavages; ●——●, pre-operative antibiotics (9 patients); ●– – –●, pre-operative antibiotics, after two lavages*

bowel, appendicular or colonic origin. The selection of patients to receive antibiotics before operation was not random: they were given to those in whom there was clinical concern about any delay in initiating treatment. Thus, although the lack of randomization may be thought to weaken our conclusion regarding the effect of pre-operative antibiotics, any bias was against the treated group. Furthermore, lack of randomization in respect of pre-operative antibiotics is irrelevant to our conclusion regarding the effect of tetracycline lavage.

The difference in the concentration of viable organisms and the impairment in bacterial growth in the systemic antibiotic group is attributable to the presence of antibiotics in the peritoneal fluid although antibiotic levels in the fluid were not measured. The timing of operation and taking of the bacteriological samples in relation to the administration of the pre-operative systemic antibiotics was not constant and varied between 2 and 8 h. We do not think that this variability, inherent in resuscitation and emergency surgery, detracts from the validity of observations which reflect a clinical situation rather than a laboratory experiment. It would, however, be interesting to examine the relationship between the concentration and growth pattern of organisms and the concentration of antibiotics in peritoneal fluid.

All the enterobacteria and all the anaerobes isolated were sensitive to cefotaxime and metronidazole respectively on routine sensitivity testing. None the less, bacterial growth in peritoneal fluid, though impaired, still occurred after pre-operative systemic antibiotics. The effect of systemic antibiotics on bacterial growth was temporarily augmented by the dilutional effect of saline lavage on the concentration of organisms in the peritoneal fluid.

In contrast, lavage with tetracycline abolished bacterial growth in peritoneal fluid. The dilutional effect of saline lavage is clearly and dramatically enhanced by the addition of a high concentration of a non-toxic broad spectrum antibiotic. Complete inhibition of bacterial growth occurred despite the relatively limited spectrum of tetracycline. Although 54 per cent of aerobes and 42 per cent of anaerobes in the present series of

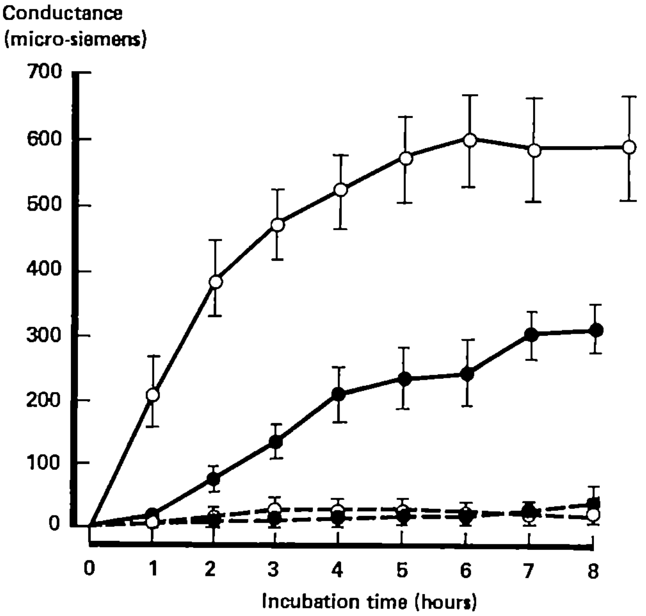

Figure 5 *The effect of tetracycline lavage on bacterial growth in 14 patients: ○——○, no pre-operative antibiotics (9 patients); ○– – –○, no pre-operative antibiotics, after two lavages; ●——●, pre-operative antibiotics (5 patients); ●– – –●, pre-operative antibiotics, after two lavages*

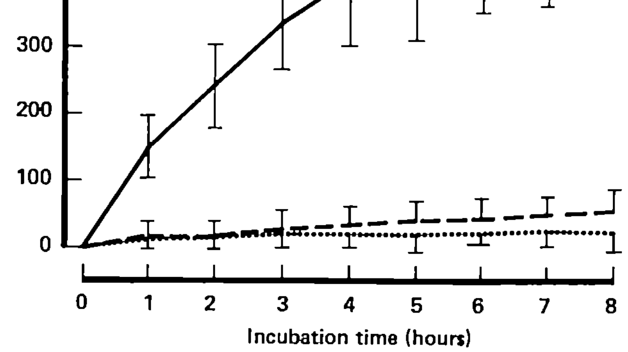

Figure 6 *The effect of tetracycline lavage on bacterial growth after 1 h in six patients: ———, initial sample; ·····, after two lavages; – – –, after 1 h*

patients were insensitive to tetracycline on conventional testing, the efficacy of tetracycline depends on its high topical concentration (1 mg/ml) in the peritoneal cavity. It has been shown previously that at such levels sensitivity is extended to include all aerobic and anaerobic intestinal pathogens[7,8].

The combination of systemic antibiotics to which all the enterobacteria and anaerobes were sensitive together with saline lavage did not result in an antibacterial action that was in any way comparable. The efficacy of such a combination no doubt varies with dose and timing of administration of antibiotics in relation to operation and sampling, and further study might show that the timing of operation could be made optimum in this respect. It is unlikely, however, that such manipulation, even if feasible in clinical practice, could assure the abolition of bacterial growth in the peritoneal exudate, an effect which is simply achieved with tetracycline lavage.

The effect of tetracycline lavage is attributable to a very high topical concentration of antibiotic. Immediately after lavage this concentration is 1 mg/ml and though we have not defined the time course of elimination of the antibiotic from the peritoneal cavity the concentration will inevitably decline with absorption and dilution. The observed abolition of bacterial growth *ab initio* may not persist with time. However, in six patients in whom further samples were taken 1 h later, bacterial growth was still abolished. The possibility that recrudescence of growth may occur after several hours remains but in practice tetracycline lavage is repeated before closing the abdomen.

In conclusion, if the primary treatment of peritonitis is ineffective the mortality is high[9]. It is important, therefore, that antibiotic strategy is optimum at the outset. On the basis of the present observations, systemic antibiotics should be given as soon as a diagnosis of peritonitis is made. In addition, tetracycline lavage abolishes bacterial growth in the peritoneal fluid and is associated with low morbidity and mortality[10]. This study gives objective evidence for its continued use as an important adjunct to conventional management.

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Plunging ranula: a report of three cases and review of the literature

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Three cases of plunging ranula are reported and the literature reviewed. Extravasation of saliva from the sublingual gland due to trauma or obstruction of its ducts appears to be the most likely cause of plunging ranula. Available data suggest that the submandibular gland is usually not involved, although at the time of surgery it may be extremely difficult to exclude a submandibular origin of the cyst in the neck. Communication between the oral and cervical components of the plunging ranula probably occur via a hiatus in the mylohyoid muscle. Such communication passing directly into the submandibular compartment may simulate submandibular gland involvement. Since 1910, 139 procedures in 89 patients with plunging ranula have been reported in the English literature. The recurrence rate was 70 per cent after incision and drainage of the cyst, 53 per cent after marsupialization, 85 per cent after excision of the cyst in the neck and 2 per cent after excision of the sublingual gland via the cervical or intra-oral route. This review suggests that excision of the sublingual gland with intra-oral drainage of the cervical swelling appears to be the treatment of choice for the plunging ranula.

Keywords: Plunging ranula

Ranula describes the bluish, translucent cystic swelling that occurs in the floor of the mouth. Occasionally an oral ranula gives rise to a cervical extension which is then termed a plunging ranula. Three cases of plunging ranulas are presented and the literature reviewed. Uncertainty with regard to the exact aetiology and pathogenesis of the plunging ranula has resulted in controversies in surgical management.

Case reports

Case 1

A 20-year-old man presented with a 2 year history of a painless swelling in the right submandibular region, which developed 6 months after marsupialization of an oral ranula. Examination revealed scarring in the floor of the mouth and an 18 × 10 cm cystic swelling in the right side of the neck. Aspiration yielded straw-coloured fluid with an amylase content of 1183 units/l. The cyst which appeared to be originating from the submandibular gland was excised with both the sublingual and submandibular glands through a cervical incision. Follow-up at 3 months showed no evidence of recurrence.

Case 2

An 18-year-old man presented with a 4-month history of an oral swelling which had ruptured spontaneously one month before the present admission. Examination revealed a cystic swelling in the floor of the mouth associated with a swelling on the left side of the neck. At surgery the sublingual and submandibular glands were removed via a left cervical incision. Follow-up at 2 years showed no evidence of recurrence.

Case 3

A 15-year-old male presented with a 5-year history of swelling in the floor of the mouth which had discharged spontaneously on two occasions. Eight months before the present admission, marsupialization of the oral cyst had been performed. Examination revealed a cystic swelling in the left submandibular triangle associated with a swelling in the floor of the mouth. The sublingual and submandibular glands were excised through a cervical incision and the cyst cavity aspirated. The patient was free of recurrence at 2 years.

Histology in all three patients showed an inflammatory wall to the cyst with no true epithelium.

Discussion

Controversy over plunging ranula has revolved around the pathogenesis and management of this condition. Although several authors[1,2] have supported Thompson's[3] postulate that the plunging ranula originates from a cervical sinus in a manner similar to that of a branchial cleft cyst, the raised amylase content of the cyst fluid[4], the initial intra-oral presentation of the ranula and the characteristic absence of a true epithelial lining has refuted this theory.

Currently it is accepted that the plunging ranula is of salivary gland origin[5]. Early authors[6,7] thought that it was a retention cyst of the sublingual or submandibular glands that had gravitated into the neck. However, the plunging ranula is now thought to be due to mucous extravasation into the tissues from a traumatized sublingual gland or ducts[4,8].

Ranula formation has been described in association with congenital anomalies[9], trauma[10] and disease of the sublingual gland[11]. Bhasker *et al.*[12] showed that partial severance of the feline sublingual duct produced mucous extravasation with sialocoele formation. Harrison and Garrett[8] produced sialocoeles following ligation of the feline sublingual duct presumably as a result of mucous extravasation from ruptured acini secondary to excessive secretory back pressure. These series of experiments failed to produce mucocoeles following ligation of the parotid or submandibular ducts[8].

The differences in response of the major salivary glands to conservative treatment following glandular injury or ductal obstruction have been explained on the basis of their differing secretory physiology. Naturally occurring plunging ranula probably occur from the sublingual gland which secretes continuously during the interdigestive period[13]. In contrast the parotid and submandibular glands secrete after major stimuli such as eating[13]. Sialocoeles following parotid trauma resolve when the patient is starved[14] and ligation of the duct produces atrophy of the gland[15].

Obstruction of the submandibular duct leads to retention cyst formation. Trauma to the gland may lead to sialocoele formation[10]. The two reported cases[5,10] of sialocoeles from the

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Table 1 *Summary of the operative experience on 89 cases (including our 3 cases) reported in the English literature since 1910*

Surgical procedure	Total number of operations	Reported number of recurrences	Reported number with successful outcome with less than 1 year follow-up	Reported number with successful outcome with at least 1 year follow-up
Incision and drainage	17	12	5	0
Marsupialization or other oral procedure	19	10	5	4
Cervical excision of cysts	33	28	5	0
Cervical excision of cyst combined with excision of the sublingual gland	26	1	13	12
Intra-oral excision of the sublingual gland and drainage of the cyst	14	0	2	12
Radiation therapy to neck	30	1	25	4
Total	139	52	55	32

References 1–4, 6, 7, 18–21, 24–41

submandibular gland were secondary to iatrogenic injury, and both resolved on conservative management. A follow-up pertechnetate scan in one case[10] showed atrophy of the gland. Thus, while this review suggests that the submandibular gland is usually not the cause of a naturally occurring plunging ranula, its role in the pathogenesis of the plunging ranula has not been completely excluded.

The oral and cervical components of the plunging ranula probably communicate through naturally occurring defects in the mylohyoid muscle. Prolongation of fat or sublingual gland through such defects into the submandibular compartment occur in up to 36 per cent of the normal population[16]. The intimate relationship between sublingual and submandibular glands[17] accounts for the intra-operative difficulty[18,19] in deciding which gland is giving rise to the plunging ranula (Case 1). This complex interrelationship also explains the danger of injury to the sublingual gland during surgical excision of the submandibular gland[20,21,30] and injury to the submandibular gland during sublingual gland excision[5,10].

The sequence of events giving rise to a plunging ranula is probably as follows:

Trauma, infection or disease may result in injury to the sublingual ducts or gland. Alternatively obstruction from atretic[22] or abnormal ducts[4] may lead to acinar rupture from excessive secretory back pressure[8].

Continuous extravasation of saliva from the injured gland into the floor of the mouth with its associated inflammatory reaction[23] results in the formation of an oral ranula.

Rising tension from continuous extravasation commonly leads to rupture of the oral ranula. However, it may also open up a potential hiatus in the mylohyoid forcing the saliva to extravasate into cervical tissue planes. Marsupialization or other surgical procedures for oral ranula may cause cicatrization in the floor of the mouth. The extravasated saliva cannot now be accommodated by the expansion of the oral compartment and is forced into the neck through the hiatus in the mylohyoid muscle. The saliva in the neck is limited by an inflammatory membrane and presents clinically as a plunging ranula.

Management

Management of plunging ranula over the years has paralleled the theory of pathogenesis in vogue at the time. *Table 1* lists all the various reported procedures and results. Eight-nine cases with an average of 1·5 operative procedures per case have been reported in the English literature. As recurrences are frequent, a follow-up period of at least 1 year is necessary. Radiation therapy, incision and drainage and marsupialization have all fallen into disrepute. Excision of the sublingual gland appears to be essential for cure[4,5] as clearly shown in *Table 1*. The single reported recurrence after sublingual gland excision was due to incomplete excision of the gland[29].

When faced with cystic swelling in the neck, it is tempting to explore it through a cervical approach. However the amylase content of the cyst[4] and a history of oral ranula should make the diagnosis of a plunging ranula obvious. The cervical approach, as used in our patients, gives access to both the sublingual gland and the cyst. Excision of the submandibular gland facilitates exposure of the sublingual gland with this approach[18]. However, extensive dissection of the cervical cyst is probably unnecessary[4,21] and often tedious as there is no true capsule and the cyst tends to burrow into cervical and parapharyngeal tissue planes. Recent reports indicate that intra-oral excision of the sublingual gland with oral drainage of the cervical cyst is adequate treatment[4,21]. Care must be exercised to avoid damage to the lingual and hypoglossal nerves and the submandibular gland and duct.

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Management of parotid sialoceles: a simple surgical technique

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Most post-traumatic parotid sialoceles can be managed conservatively with repeated aspirations and compression[1–3]. However, if a sialocele is resistant to this form of treatment a more aggressive approach is necessary. Re-exploration of the wound and ligation of the proximal duct, tympanic neurectomy, superficial or total parotidectomy, and irradiation, are some of the suggested radical forms of management[2–4]. These are obviously major procedures with significant risks. In the present paper a simple and effective alternative is described.

Method

The procedure can be performed under local or light general anaesthesia. The cyst is opened by means of a 0·5 cm incision on the overlying skin. A small forceps is forced through the base of the cyst and through the masseter into the mouth. With the help of this forceps a 5 cm long Jacques catheter (EG 6) is positioned with one end in the sialocele and the other end in the mouth. The tube is secured by suturing it to the mucosal surface of the cheek. The skin incision is sutured and a compression dressing is applied. The patient is put on oral penicillin and antiseptic mouthwashes. Oral mixed fluids are given for the first 2 days and thereafter a light diet. The tube is removed 3 or 4 days after it stops draining saliva (about 10 days after the insertion).

Discussion

We used this technique in two patients with post-traumatic sialoceles. In both cases a conservative approach consisting of repeated aspirations and compression over a period of 8–10 weeks had failed. Because of thinning of the overlying skin and imminent external rupture, it was decided to perform the operation described above. The tube drained saliva for 5 or 6 days and then stopped. The sialocele disappeared completely and the artificial internal orifice closed within days of the tube being removed. Three-months later there was no recurrence and the cosmetic results were excellent. A parotid scan showed significant atrophy of the affected parotid.

In conclusion we have described a simple technique of managing traumatic sialoceles resistant to conservative treatment. It is easy, effective and can be performed under local anaesthesia.

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Splenic injury: a prospective multicentre study on non-operative and operative treatment

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One hundred and forty-seven patients with splenic injury admitted to 18 different hospitals were included in a prospective multicentre study. The spleen was saved in 64 per cent. Out of the total series, 43 per cent of patients were not operated upon, 5 per cent had exploratory laparotomy only, and in 16 per cent splenic repair was performed. Treatment is discussed with reference to the nature of the splenic lesion, concomitant injuries, amount of blood transfusion given, and age of the patient. No deaths were definitely related to the splenic injury. The frequency of serious recurrent bleeding was not higher in the splenic salvage group when compared with the splenectomy group. Delayed bleeding was detected in 4 per cent of the patients. The mode of treatment varied considerably in different hospitals in that conservative treatment was performed in 14, splenic repair in 10 and splenectomy in 12 hospitals. Splenic salvage seems safe in most patients with a splenic injury. However, meticulous surveillance of the patient is mandatory.

Keywords: Splenic trauma, non-operative treatment, splenic repair, delayed bleeding

About 2 per cent of children undergoing splenectomy after trauma may die subsequently from septicaemia, a development which, in these patients, has an alarming mortality rate of 50 per cent[1]. The issue of septicaemia in splenectomized adults is not so obvious[2–4] and in one large retrospective study the increase in death rate was due only to pneumonia and cardiac infarction[5].

It has been pointed out that an injured spleen can either heal spontaneously[6] or be successfully conserved by a variety of operative techniques[7–10]. In Norway, Solheim has for some years advocated splenic salvage after trauma[11], and a number of reports on splenic conservation have originated from departments with a special interest in splenic surgery. The majority of such reports concern injuries in children, and there have been no reports on the results of such treatment when this is carried out in departments with little experience in this field.

A multicentre registration of traumatic injury of the spleen was therefore initiated to evaluate the results of splenic salvage in every-day surgery.

Materials and methods

The treatment of splenic injuries was documented prospectively from November 1982 to January 1985 in 18 Norwegian hospitals. The hospitals included most of the university and central hospitals in the country (*Table 1*), but all participating hospitals also serve as district general hospitals. The study comprised 147 patients (110 men and 37 women) who had suffered blunt abdominal trauma. Approximately 65 per cent of the patients were treated in university hospitals located in the more densely populated areas, 25 per cent in central hospitals and 10 per cent in county hospitals. The patients were treated according to the guidelines of each particular hospital. The procedures were reported on a standard mutually agreed form.

A diagnosis of splenic injury was obtained by exploratory laparotomy, ultrasonography, splenic scintiscan or computerized tomography (CT).

Three main groups of patients were classified according to the treatment: non-operated, operated but with splenic salvage (conservative surgery), or splenectomy. The mean age of the patients in the non-operated group was 22±16 years (range 3–81). The group undergoing conservative surgery had the lowest mean age, namely 17±7 years (range 5–37) and the splenectomy group had the highest (27±19 years, range 4–75). The percentage of patients under the age of 16 years in the three groups was 49, 45 and 11 per cent respectively.

Most of the patients were followed by outpatients' review 3 weeks after the injury. Some also had a scintiscan or ultrasound examination at that time.

Results

Treatment

The spleen was conserved in 94 patients (64 per cent) (*Table 2*). Sixty-three of the 147 patients (43 per cent) were treated non-operatively, while conservative surgery was performed in 31 patients. Eight of these operated patients had an exploratory laparotomy without splenic manipulation; at operation the bleeding had ceased in seven, and was minimal in one.

Among the 23 patients undergoing 'splenic repair' the most frequent procedure was suturing of fractures (19 patients). Teflon pledglets to prevent the sutures from tearing the spleen were used on only three occasions. Partial resection was carried out in four patients; as a result of fragmentation 80 per cent of the organ was removed from one of these. In another patient both resection and suturing were performed. The splenic artery was ligated in three patients, in one of whom it was the only surgical procedure. In two other patients, smaller arteries were

Table 1 *Number of participating hospitals in the different categories and number of patients treated*

Hospital category	Hospitals (*n*)	Patients (*n*)
University	6	91
Central	6	40
County	6	16
Total	18	147

Table 2 *Total number and percentage of patients with multiple trauma in each treatment group*

	Non-operated	Conservative surgery	Splenectomy
Total (*n*)	63	31	53
Multitraumatized (%)	24	35	53

Table 3 *Delay (days) from trauma to hospitalization in the different groups of treatment for 22 patients not immediately admitted after splenic injury*

Delay	Non-operated	Conservative surgery	Splenectomy
1	8	1	3
2	1	0	0
3–4	3	0	0
6–7	1	0	2
9–11	1	1	0
28	0	0	1

Table 4 *Nature of splenic injuries in the different treatment groups*

	Non-operated	Conservative surgery	Splenectomy
Capsular tear	0	7	2
Contusion	6	0	0
Haematoma	26	0	2
Fracture	35	25	34
Fragmentation	0	1	16
Vascular injury	0	0	4

Table 5 *Distribution of 120 lesions in 86 patients with concomitant injuries*

Thoracic		Abdominal		Other	
Ribs only	27	Renal	14	Cranial/cerebral	13
Lungs/pleura	27	Ureter/bladder	2	Extremities	12
Heart	3	Liver	7	Spine/pelvis	6
		Gut	2		
		Retroperitoneum	7		

ligated. Microfibrillary collagen was applied in some patients to stop the oozing of blood.

Conservative surgery was the first line of treatment in only 6 of the 53 splenectomized patients. Two patients had splenomegaly due to chronic lymphatic leukaemia and infectious mononucleosis, and splenic salvage was not attempted.

Delayed bleeding

Twenty-two patients were admitted between 1 and 28 days after the accident. Sixteen patients had a delay of less than 5 days and possibly should not be considered as genuine examples of delayed rupture (*Table 3*). In this group, 12 of the 16 were treated non-operatively and 3 were splenectomized. On the other hand, only two of six patients with a delay of more than 5 days were treated non-operatively while four were splenectomized. One patient with initially successful non-operative treatment was splenectomized for other reasons after 14 days.

It might be expected that surgery would be performed on the more seriously injured patients. The mode of treatment was therefore related to the nature of the splenic injuries and the frequency of associated injuries, as well as to the amount of blood transfused.

Nature of lesions

The nature of the splenic lesions in the different treatment groups is given in *Table 4*. Fracture was the most frequent diagnosis in all groups. Intrasplenic or perisplenic haematomas were nearly as frequent as fractures in the non-operated group. In the patients having conservative surgery, splenic fracture was found in approximately 75 per cent, and a torn splenic capsule was found in nearly 25 per cent. Fragmentation was seen in about 30 per cent of the removed spleens. In only one patient with a fragmented spleen was conservative surgery performed. Bleeding hilar vessels were found solely in the splenectomy group (nearly 10 per cent).

Eighty-six patients had one or more concomitant injuries totalling 120 lesions (*Table 5*). Fracture of the ribs and lung injuries were the most frequent, followed by skeletal fractures, then renal and cranial and/or cerebral trauma. Seven patients with injuries of the liver did not require operative intervention. Two patients had perforation of the gut (one small intestine, one small and large intestines plus gallbladder), another had injury to a ureter and a fourth had rupture of the urinary bladder. Two patients had uncomplicated injury to the pancreas, and five had minor retroperitoneal bleeding.

Not unexpectedly nearly twice as many patients (53 per cent) in the splenectomized group suffered multiple trauma compared with the number of patients treated non-operatively (24 per cent), while the frequency in the group undergoing conservative surgery was 35 per cent (*see Table 2*).

The amount of blood transfusion given to the patients without multiple trauma in each treatment group is shown in *Table 6*. The sum of pre- and peroperative units is given for the operated patients. Approximately 7 per cent of the conservatively treated patients received blood transfusion. In the exploratory laparotomy group, two out of three, and in the splenic repair group, eight out of seventeen, received two units or less. In the splenectomy group only 23 per cent of the patients were given two units of blood or less.

The influence of age on treatment was examined by studying patients above and below the age of 16 years and comparing the relative number within the different treatment groups. The frequency of non-operation was nearly twice as high in the younger group as in the older age group, while four times as many older patients were splenectomized (*Table 7*). In the group of patients under 16 years, 85 per cent had not suffered multiple trauma, compared with 53 per cent of those over 16 years of age (*Table 8*). The trend towards more radical treatment in older patients was also apparent among the group who had not experienced multiple trauma, although this was not so pronounced as in the total patient population.

The need for blood transfusion also appeared to be lower in the younger patients. Nearly three-quarters of the patients

Table 6 *Number of units of blood transfused in patients without multiple trauma in the different treatment groups*

Transfusion (units)	Non-operated	Exploratory laparotomy	Splenic repair	Splenectomy
0	43	1	5	2
1–2	2	1	3	3
3–4	1	1	5	12
5	0	0	4	5

Table 7 *Age distribution of patients in the different treatment groups*

Age (years)	Total	Non-operated	Conservative surgery	Splenectomy
<16	51	31 (61)	14 (27)	6 (12)
>16	96	32 (33)	17 (18)	47 (49)

Figures in parentheses are percentages

Table 8 *Age distribution of patients without multiple trauma within each treatment group*

Age (years)	Total	Non-operated	Conservative surgery	Splenectomy
<16	41	25 (61)	11 (27)	5 (12)
>16	51	23 (45)	9 (18)	19 (37)

Figures in parentheses are percentages

Table 9 *Age distribution of patients without multiple trauma given blood transfusion*

Age (years)	Total	Transfusion (units) 0	1–2	3–4	>5
<16	41	30 (73)	6 (15)	4 (10)	1 (2)
>16	51	26 (51)	3 (6)	15 (29)	7 (14)

Figures in parentheses are percentages

without multiple trauma did not receive any transfusion, while it was necessary in approximately one-half of the patients in the older age group (*Table 9*). In accordance with this, 14 per cent in the older group received 5 units of blood or more compared with 2 per cent in the younger age group.

Complications

The splenic injury was not considered to be the cause of death in any patient. However, one patient in the splenectomy group died from gangrene of the small intestine which might have been the result of hypotension caused by bleeding from the injured spleen. Three patients in the same group died from concomitant injuries—one from cardiac rupture and two from head injuries.

Two cases of life-threatening recurrent bleeding occurred in the non-splenectomized groups. A child with increased intra-abdominal fluid on ultrasonography and a suspected splenic injury started bleeding on the fifth day after admission. She recovered after resection of the fragmented spleen. One patient started bleeding again a few hours after suture of a splenic fracture, and the spleen had to be removed. The bleeding appeared to arise from an overlooked fracture line.

Two splenectomized patients were reoperated upon because of haemorrhage within the first postoperative day. One of these had a life-threatening bleeding from the pancreatic tail which required a massive blood transfusion.

Other non-lethal complications in the splenectomized group were one case of septicaemia, an intra-abdominal abscess which was drained, one urinary infection and one pulmonary embolism. In the non-operated group four patients developed pneumonia and one had a urinary tract infection.

The non-operated patients without multiple trauma were hospitalized for a mean of 11±8 days. The corresponding figures for the patients undergoing conservative surgery and for the splenectomized patients were 10±3 days and 8±5 days respectively.

Inter-hospital variation

There was a great variation in number of patients treated by each hospital. Ten hospitals had only two or three cases, while five hospitals had 12 or more (*Table 10*).

There was a marked variation in treatment. In the five hospitals with the greatest number of patients, the per centage of non-operated patients varied from 0 to 80 per cent and the percentage of splenectomized patients from 20 to 71 per cent (*Table 10*). In the hospital where splenectomy accounted for 20 per cent of the cases, no splenic repair was done. The incidence of these procedures varied from 10 to 50 per cent in the other hospitals. Exploratory laparotomy without any splenic manipulation was mainly limited to one hospital. Non-operative treatment was performed in 14 hospitals, splenic repair in 10, and splenectomy in 12 of the 18 hospitals.

The number of patients with multiple trauma in the various hospitals varied from 17 to 62 per cent.

Discussion

A number of publications from departments obviously interested in splenic conservation claim that conserving the injured spleen may be a safe procedure[7–12]. Whether safety depends on obtaining treatment in specially trained units could not be determined from the literature. A prospective study on splenic trauma as treated in 18 different surgical departments was therefore carried out. As a randomized study could not be performed, for ethical reasons, each department treated their patients according to their own guidelines; these were changed to a more conservative approach during the study in three of the 18 hospitals. We suggest that the present study represents the results of treatment of splenic trauma in average surgical departments.

Table 10 *Total numbers of patients treated in five different hospitals. The distribution between the treatment groups and the proportion of patients with multiple trauma is given as percentage of the total number treated in each hospital*

	Hospital A	B	C	D	E
Total number (*n*)	35	21	19	14	12
Non-operated (%)	80	10	47	0	17
Exploratory laparotomy (%)	0	29	0	7	0
Splenic repair (%)	0	10	21	21	50
Splenectomy (%)	20	52	32	71	33
Multitraumatized (%)	37	62	21	21	17

In the 147 patients, splenic salvage was accomplished in 64 per cent, after non-operative treatment (63 patients), splenic repair (23 patients) or exploratory laparotomy (8 patients). Splenectomy was performed in 53 patients. There was no mortality due to the splenic injury, indicating that, when properly treated, this injury is rarely life-threatening.

In this multicentre study there was clearly a relationship between the magnitude of injury and the treatment given. Twice as many patients in the splenectomy group had multiple trauma compared with the non-operated group. Extensive injury to the spleen with fragmentation nearly always resulted in splenectomy. While the majority of the patients in the non-operative group did not receive any blood transfusion, the majority of splenectomized patients received three or more units.

Compared to recent reports from single centres[12–14], the frequency of non-operation (43 per cent)[13,14] and splenic repair (16 per cent) was high in the present study. While this may reflect a difference in attitude towards the treatment of splenic injury, it cannot be ruled out that as a consequence of a thorough search for splenic injury we included patients with less extensive injuries than those in previous reports. Another point of importance may be the relatively high percentage of patients under 16 years of age in our study. These patients had a lower incidence of multiple trauma and received less blood transfusion than the corresponding older patients, suggesting a greater tendency to spontaneous cessation of bleeding in younger patients[15].

An indication for splenectomy has been the risk of rebleeding during or after splenic salvage. In this study recurrence was only seen once in the initially non-operated group—an incidence of rebleeding of 1·6 per cent. However, this was a nearly fatal case in a small child who re-bled on the fifth day after injury. This low frequency of recurrent bleeding is similar to that of one other report[13], and is considerably lower than that reported by Malangoni *et al.*[14]. In the present study, with a relatively high frequency of operative splenic repair, recurrent bleeding was seen in only one such patient (4·2 per cent). There was no haemorrhage due to slipping or cutting out of sutures in spite of the use of Teflon pledglets in only 3 of 19 suturing procedures.

Delayed bleeding is a complication of splenic trauma. It cannot be ruled out in patients admitted a few days after the accident who may be bleeding slowly from the injured spleen. On the other hand, it seems likely that admission after the fifth day must be the result of delayed bleeding. Thus, the frequency of delayed bleeding in this study ranges from 4 to 15 per cent. The first figure corresponds well with that of a previous report[16]. Delayed bleeding appearing 2 weeks or more after the accident was rare and occurred only once, arising as late as 4 weeks after the trauma.

As two-thirds of the patients with a delay in hospitalization of 5 days or more were splenectomized, it seems that there is a relatively small chance that true delayed bleeding may cease spontaneously. However, the small number of patients in this study does not allow a definite conclusion on this point.

Bleeding ceased spontaneously in 48 per cent of patients, including the 63 treated non-operatively and the 8 undergoing exploratory laparotomy. Thus there seems to be a good chance of spontaneous cessation of bleeding after splenic injury as well as a minor risk of recurrent bleeding after splenic salvage. We therefore suggest that in a patient with a stable circulatory status some blood transfusion should be allowed before deciding on operation. In the present study 15 patients operated upon received two or less units and could possibly have avoided surgery; thus 59 per cent would have been treated non-operatively. If, according to the same criteria, the five splenectomized patients who received two or less units of blood had not come to splenectomy, the frequency of splenectomy might have been reduced to 28 per cent. In fact, conservative surgery was the primary treatment in only 6 of 53 splenectomized patients.

The issue of blood transfusion in patients with splenic injury does not seem to be extensively discussed in the literature. However, it has been suggested that as many as four units of blood could be given over a 48 h period in adults[13].

In addition to dangerous bleeding, opponents of conservative treatment of splenic injury have feared the possibility of delayed diagnosis of other serious intra-abdominal injuries. In the present study, such injuries occurred in only 5 per cent of cases and there was no important delay in treatment. However, this study did not record delayed laparotomies due to an erroneous diagnosis of splenic damage. Thus, although it suggests that a conservative approach to splenic injury will not delay the diagnosis of other serious intra-abdominal damage, this is not conclusive. While development of splenic pseudocysts has been feared as a consequence of conservative management, this is a rare complication[17].

The low incidence of recurrent haemorrhage supports the idea that patients with splenic rupture treated without splenectomy may be discharged from hospital shortly after the abdominal symptoms and signs have disappeared. Remembering the slight but real danger of delayed bleeding, we would suggest that the patients should be told to consult a doctor immediately should abdominal pains recur during the first weeks after discharge. It would also be prudent to retain those patients who live far from the hospital for a longer period.

It has been argued that splenic salvage leads to a longer stay in hospital. In the present study the mean duration of hospitalization for non-operated patients who had not suffered multiple trauma was only 3 days more than for those who had splenectomy. This should therefore not be a major argument against conservative treatment.

When comparing data from the various hospitals there are conspicuous differences in the modes of treatment. The fact that in one hospital 80 per cent of the patients were treated conservatively, while in another hospital all 14 patients were operated upon, cannot merely be explained by a more thorough search for splenic trauma in the former department. It may in part be due to a difference in opinion regarding the safety of observing patients with splenic trauma, and perhaps reflects a difference in opinion as to the importance of splenic salvage and the safety of conservative surgery.

On the whole, non-operative treatment was well accepted and was carried out in 14 of the 18 participating hospitals. There may be a slightly greater scepticism regarding splenic repair, which was carried out in 10 hospitals, while splenectomy was performed in 12 hospitals. Ten hospitals treated only two or three patients, and no departments reported more than six splenic repairs. This means that both non-operative treatment and splenic repair have been successfully carried out in departments with little experience in this area.

This multicentre study confirms the results from single centres that splenic salvage is a relatively safe procedure. In a patient with a splenic injury with a stable circulation, it seems reasonable to try non-operative treatment with blood transfusion before proceeding to operation. If bleeding from a minor fracture has ceased at laparotomy, the spleen can either be left untouched or a pad of microfibrillary collagen applied. In cases of slight bleeding conservative surgery can be performed. However, splenic salvage requires thorough observation of the patient. It is suggested that a bleeding spleen should be removed if the condition of the patient demands a minimal operation time, or if the surgeon feels uncertain about the result of a salvage operation in a patient who will not tolerate a reoperation for recurrent bleeding. Splenic salvage should be the goal, but not at all costs.

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Major causes of intestinal obstruction in Libya

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The object of this study is to focus attention on the causes of intestinal obstruction in Libya. In this study, spread over 30 months and involving 114 patients, the most common cause was the entrapment of bowel in an external hernia. Postoperative adhesions accounted for obstruction in a third of our patients, and 59 per cent of them followed appendicectomy. Biliary lithiasis is the most common surgical disease in Libya, yet there was only one instance of gallstone ileus in this series. Sigmoid volvulus and intestinal lymphoma were also rare, and tubercular stricture and Crohn's disease were remarkable by their absence. There were no cases of idiopathic intussusception during or immediately following Ramadan.

Keywords: Intestinal obstruction, Libya, adhesive disease

Regional variations in the pattern of disease and alterations in the disease spectrum with the passage of time are well documented. This makes it essential that studies are made periodically in every region to define local health problems. With this in view, we have studied the pattern of intestinal obstruction in Benghazi, Libya.

Benghazi is the second largest city in Libya. The entire emergency surgical work of the city and the neighbourhood is catered for by the Al Jala Hospital. There are other major hospitals in the city but they do not handle emergency surgery. Even if patients in such hospitals develop an acute problem, they are promptly transferred to Al Jala Hospital. Thus this study gives precise information on the pattern of intestinal obstruction in our community.

Materials and methods

The case files of all patients operated on between 1 January 1984 and 30 June 1986 with a provisional diagnosis of intestinal obstruction were collected. From these were selected the files which showed that the patient had intestinal obstruction and we then abstracted the cause, the site of obstruction, the treatment offered and the outcome. We thus compiled a series of 114 patients.

Routine minor and medium range emergency surgery is carried out in this hospital by the house staff headed by a surgeon of registrar grade. They perform appendicectomies and repair of hernias but do not perform bowel resections. All major procedures are performed by a consultant surgeon.

Age and sex distribution

The male:female ratio in the population is 103:97 but when the age pyramid is considered it is found that at the extremities of life this ratio is reversed (1973 census). *Table 1* shows the age and sex distribution of our patients with intestinal obstruction. Male predominance is apparent throughout the series but is more pronounced in the aged and the very young.

Causes and sites of obstruction

Table 2 shows the causes of intestinal obstruction. External hernias were the most common cause, followed by postoperative adhesions. However, if all patients who developed intestinal obstruction after surgery are grouped together, they outnumber those who had obstruction due to entrapment of bowel in external hernias.

The disparity in the figures in *Table 2* is due to overlap. Three patients with secondary deposits of neoplasia (two from melanoma and one from lung carcinoma) and one patient with the Peutz–Jeghers syndrome were also included under intussusception. Meckel's diverticulum accounted for two further cases of intussusception, and in the seventh patient in this group no cause was obvious.

There were 97 patients in whom the obstruction was mechanical Sixty-nine had small bowel obstruction, thirteen had large bowel obstruction. In the remaining patients the obstruction was combined and multiple.

Relationship between adhesions and previous surgery

The initial operations responsible for the development of intestinal obstruction due to adhesions, are shown in *Table 3*. Appendicectomy was the outstanding cause of adhesive obstruction.

Table 1 *Age and sex distribution of patients with intestinal obstruction*

	Age							
	0–12	13–20	21–30	31–40	41–50	51–60	61–70	71+
Male	9	15	9	13	10	12	5	9
Female	2	7	5	5	7	3	1	2

Table 2 *Cause of obstruction in 114 patients*

External hernias ($n=35$)	
Inguinal	18
Femoral	8
Para-umbilical	7
Others	2
Postoperative causes ($n=41$)	
Adhesions	32
Paralytic ileus	4
Anastomotic stricture	2
Incisional hernia	2
Phytobezoar	1
Neoplasms ($n=12$)	
Primary	9
Secondary (produced intussusception)	3*
Paralytic ileus (inflammatory) ($n=10$)	
Intussusception ($n=7$)	
Secondary growth	3
Meckel's diverticulum	2
Peutz–Jeghers syndrome	1
Cause not found	1
Mesenteric vascular occlusion ($n=3$)	
Miscellaneous ($n=10$)	
Adhesions (? cause)	2
Internal hernias	2
Ileosigmoid knotting	1
Gallstone ileus	1
Sigmoid volvulus	1
Pseudomembraneous enteritis	1
Peutz–Jeghers syndrome (intussusception)	1*
Faecal impaction	1

* Denotes overlap

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Table 3 *Previous surgery leading to intestinal obstruction by adhesions in 32 patients*

Appendicectomy	19
Cholecystectomy	3
Surgery for penetrating abdominal trauma	3
Surgery for blunt abdominal trauma	2
Peptic ulcer surgery	2
Surgery for ruptured ectopic pregnancy	1
Surgery for malignancy	1
Colectomy and ileorectal anastomosis for ulcerative colitis	1

Procedures undertaken

The obstruction was relieved in most patients by simple procedures such as opening the neck of an inguinal hernia, separation of adhesions or division of bands. However, bowel resection became necessary in 23 of the 114 cases (20·2 per cent). Eleven had strangulated non-viable bowels. Five patients had easily resectable neoplasms; four of them were treated by primary resection and anastomosis, and in the fifth patient a left hemicolectomy and defunctioning transverse colostomy were performed. Three patients with secondary growths causing intussusception underwent resection and anastomosis. In two cases of anastomotic stricture, the stenotic segment had to be resected and a fresh anastomosis made. A segment of jejunum was resected in a patient with the Peutz–Jeghers syndrome. Injury during surgery was responsible for resection in the last of these 23 patients.

Bypass procedures were performed in three instances. In two of them, the object was to overcome obstruction due to a nonresectable neoplasm and in the third the adhesions were so dense and multiple that it was not possible to pinpoint the site of obstruction; all that was feasible was to anastomose a grossly dilated loop of bowel to the most proximal accessible portion of the collapsed segment. Proximal external drainage was performed in three cases, two with malignancy and a third with inflammatory bowel disease.

Delay between initial surgery and obstruction

There were 41 instances of intestinal obstruction in patients who had previously undergone abdominal surgery (*Table 2*). Twenty-nine (70·7 per cent) occurred within three years of surgery, 35 patients (85·4 per cent) had surgery for obstruction within five years, while the longest interval noted in the series was 23 years.

Mortality and morbidity

Eight of our patients died. Two deaths followed mesenteric vascular occlusion, two followed resection for malignancy, two followed surgery for strangulation, one followed surgery for paralytic ileus and another followed surgery for postoperative adhesions. The primary causes of death were hypovolaemic and septic shock (3), uncontrolled sepsis (2), pulmonary embolism (1), hepatic failure (1) and renal failure (1).

The major complications observed during the study were intra-abdominal sepsis requiring further surgery (4 patients), burst abdomen (4 patients) and anastomotic leak (3 patients).

Discussion

The most common single cause of intestinal obstruction was entrapment of bowel in an external hernia. It was not customary to attempt reduction of an obstructed hernia unless the patient was a poor surgical risk. It is probable that at least some of these hernias could have been reduced if this had been attempted. Adhesions as a mechanical cause of intestinal obstruction in our series (34 per cent) had a similar incidence to that of the series reported by Bevan (37·9 per cent)[1].

Sigmoid volvulus is a frequent cause of intestinal obstruction in Africa and Asia[2] but accounted for obstruction in only one of our patients. Intussusception is known to occur in some Muslim countries such as Egypt just after Ramadan[3] but was not observed in our patients. We did not encounter any patients with tubercular stricture although intestinal tuberculosis is relatively common in Asia and Africa. Crohn's disease is prevalent in western societies but was not a cause for obstruction in our series. The intestine is the most common extramedullary site of lymphoma[4]. Patients with Mediterranean Lymphoma may develop and present with acute intestinal obstruction[5] but we had only one such patient.

Gallstone disease is common in Libya and an operating day rarely passes without at least one patient being operated on for gallstones or their complications. Gallstone ileus is encountered with increasing frequency in old age[6], and 0·3–0·5 per cent of those with gall stones develop biliary-enteric fistula[7]. Yet during the study there was only one instance of gallstone ileus and none of biliary enteric fistula.

The most common emergency operation performed in Al Jala Hospital is appendicectomy. Elective and emergency hepatobiliary surgery together far outnumber appendicectomies, but there was a gross preponderance of adhesions after appendicectomy. The reasons for this may be that the peritoneal cavity in appendicitis is infected and that surgery is performed by a surgeon in training, whose handling of tissue may not be delicate. On the other hand biliary surgery is more often undertaken as an elective procedure and performed by a more senior surgeon.

The overall mortality in our series is 7 per cent. If the external hernias are excluded, the mortality figure rises to 10%. Wangensteen has observed that the mortality rises to 25 per cent in obstruction if the bowel is non-viable[8] and our experience also highlights the danger of strangulation. The policies of quick and efficient correction of anaemia and fluid/electrolyte imbalance, early surgery, and the direct involvement of a senior experienced surgeon when intestinal resection is necessary, remain the mainstays of management.

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Effects of haemorrhage on wound strength and fibroblast function

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The impairment of healing in laparotomy wounds in rats with compensated oligaemia has been studied in two parallel investigations. Animals bled 1 ml/100 g body weight (bled) were compared with unbled animals undergoing the same operation (control). Firstly, wounds were assessed after 22 days for strength of skin and muscle layers (11 control: 9 bled). Both layers were significantly weaker in bled animals; by 36 per cent for skin ($P < 0{\cdot}02$) *and by 22 per cent for muscle* ($P = 0{\cdot}02$)*. Secondly, wound fibroblast function was assessed after 10 days by quantitative histology and autoradiography (30 control: 31 bled). There were no significant differences between the two groups for fibroblast density, replication* ([^3H]*thymidine), or general protein synthesis* ([^3H]*leucine). Bled animals had less dense collagen packing by 21 per cent* ($P < 0{\cdot}01$)*, but 33 per cent more incorporation of* ([^3H]*proline by fibroblasts* ($P < 0{\cdot}01$) *compared with control animals. The effect of compensated oligaemia on wound healing is more marked in skin than in muscle; it appears to be a specific increase in collagen turnover with the increase in reabsorption exceeding that in synthesis.*

Keywords: Wound healing, haemorrhage, fibroblasts

It has been demonstrated previously[1] that blood loss insufficient to cause clinical shock (compensated oligaemia) can, if not replaced, give rise to impaired wound healing both in experimental animals and in surgical patients. Although such blood loss gives rise to either no or a transient (< 5 min) fall in blood pressure or cardiac output, it does not follow that there are not reductions of blood flow in specific regional beds. Indeed, clinical observation of, for example, a volunteer after a donation of blood would indicate that skin vasoconstriction can occur after the loss of about 10 per cent of the circulating blood volume. In an earlier study we showed that the impairment was associated with a shift to the right of the healing curve, there being no difference in the ultimate wound strength of median laparotomy scars after 3 months between animals bled 1 ml/100 g body weight at the time of surgery and unbled controls[2]. This study also showed that, although 6 weeks after laparotomy there was less densely packed and more randomly oriented collagen in the healing wounds of bled than those of control animals, there was no difference in the fibroblast density in the healing zone between the two groups. This suggested that the defect was likely to be one of fibroblast function with respect to collagen, rather than a failure of fibroblast replication or migration.

The present studies were designed to ascertain more precisely the nature of any defect of fibroblast activity in the impaired wound healing following compensated oligaemia, and the relative impairment in the skin and muscle layers of a laparotomy.

In this initial study of fibroblast function and different tissue layer strengths, the period after surgery for each investigation was different; being that at which the maximum change in the parameter was occurring. If a difference were demonstrated, then subsequent studies would need to be carried out on the complementary parameter at the two postoperative time intervals.

Methods

Two studies were carried out, both using the rat laparotomy with blood loss as described previously[2]. All the animals were healthy young adult female Porton Wistar rats, with an initial body weight of 250–350 g. The animals were anaesthetized (sodium pentabarbitone, 30 mg/kg IP), the skin of the abdomen and neck was shaved and cleaned with 0·5 per cent chlorhexidine in 70 per cent ethanol. Through a midline neck incision the left common carotid artery was exposed, ligated distally with 0·7 metric monofilament polypropylene and a second loop of the same material left untied proximally. A midline laparotomy was made from the pubis cephalad for 5–6 cm and covered with a moist swab. After opening the abdomen either the proximal carotid artery ligature was tied (control), or 1 ml blood/100 g body weight was slowly removed from the artery by syringe and needle and the proximal ligature then tied (bled), and the neck wound covered with a moist swab.

One hour after the laparotomy both wounds were closed as a single layer using interrupted vertical mattress bulk sutures of 0·7 metric monofilament polypropylene. The animals were allowed to recover and no antibiotic was given. Food (Labsure pellets) and water were available *ad libitum*, and the animals were kept in a controlled 25°C environment with a 12/12 h light/dark cycle.

The first part of the study was for wound strength and involved 11 control and 9 bled animals. After 22 days survival the animals were killed in a carbon dioxide narcosis chamber. The anterior abdominal wall was removed *en bloc* and pinned out on a board. The stitches were removed and the wound area divided into four horizontal strips, each ≈ 10–12 mm wide. Each strip was carefully separated into skin (including subcutaneous tissue) and muscle layers, the width of each strip in the relaxed state measured with vernier callipers, and the break load of individual strips determined using an Instron type 1026 tensiometer. The latter was fitted with rubber faced pneumatic grips to avoid tissue damage, and from an initial separation of 2·0 cm the specimens were extended at a rate of 50 mm/min. The break load was calculated in kg/cm. This novel method was employed, rather than the more usual wound burst strength used in our previous[2] and most other studies, in order to determine whether there was any difference in response between the skin and subcutaneous tissues, and the deeper musculofascial layer.

The second part of the study involved using three radioisotopes: [^{3}H]thymidine to estimate cell replication, [^{3}H]leucine for general protein synthesis, and [^{3}H]proline for specific collagen metabolism. A total of 30 control and 31 bled animals were studied: 20 with [^{3}H]thymidine (9 control: 11 bled), 20 with [^{3}H]leucine (10 control: 10 bled), and 21 with [^{3}H]proline (11 control: 10 bled). A greater total number of animals was used in this study in order that the numbers for each of the three isotopes used were approximately the same as those for the wound strength study. The animals were assessed after 10 days survival and for all three radioisotopes 200 μCi was injected 4 h before they were killed in a CO_2 narcosis chamber. The abdominal wall was

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excised *en bloc*, pinned out on a board and fixed in 4 per cent formaldehyde buffered to pH 7·40. The wound was divided into three approximately equal blocks. Sectioning and quantitative histology were carried out using computer aided structured random sampling and image analysis for each block. Stains used in light microscopy estimates were haematoxylin and eosin, and van Gieson: autoradiographs were exposed for 7 days and counterstained with haematoxylin and eosin.

In addition to the 71 animals in which studies were completed, 5 other animals were used; 4 were anaesthetic deaths and 1 control animal died on the second postoperative day for no demonstrable reason.

Wound break load and quantitative histology estimates for each animal were the mean of all measurements; 4 strips for break load and 48 fields for histology. For autoradiography, [^{3}H]thymidine was expressed as the percentage of fibroblasts showing uptake by the nucleus and [^{3}H]leucine and [^{3}H]proline as the number of developed particles/fibroblast.

Comparison between the two groups was by the two-tailed Mann–Whitney U test, with an upper level for significance of $P=0{\cdot}05$.

Results

The results are summarized in *Table 1*.

Wound strength (Figure 1)

The muscle layer was significantly weaker than the skin in both control and bled animals ($P<0{\cdot}02$). Both tissue layers were significantly weaker in bled than in control animals (skin, $P<0{\cdot}02$: muscle, $P=0{\cdot}02$). The mean skin break load in bled animals was 36·4 per cent less than in controls, while for muscle it was 22·2 per cent less.

Fibroblast function

The fibroblast density did not differ significantly between the two groups (*Figure 2*), neither was there any difference in the uptake by fibroblasts of either [^{3}H]thymidine (*Figure 2*) or [^{3}H]leucine (*Figure 3*). Despite the similar numbers of fibroblasts in the two groups, the healing wounds in bled animals contained significantly less collagen than the control animals ($P<0{\cdot}01$), the mean collagen packing density in bled animals being 79·3 per cent of that in control animals (*Figure 4*). This was associated with a significantly greater uptake of [^{3}H]proline by fibroblasts in bled animals (*Figure 4*), being 32·8 per cent more than in control animals ($P<0{\cdot}01$).

Discussion

The different times were selected because the maximum fibroblast density in a healing wound occurs in advance of the maximum rate of gain in wound strength. The times chosen were approximately at or just after the respective maxima[3–5].

Compensated oligaemia affected the strength of both layers of the laparotomy wound, but in this experimental model the effect was more marked on the skin than on the muscle layer (*Table 1, Figure 1*). This was reflected in the relative strength of the muscle layer as compared to skin; being 66·9 per cent for the control compared to 93·4 per cent for the bled group; but this difference just failed to reach statistical significance. In incisional hernia it is the deeper tissues only which disrupt, the skin remaining intact. Therefore, the effect on the muscle layer is likely to be of more clinical import. The decrease in musculofascial strength with compensated oligaemia in this study would imply an increased risk of incisional hernia: the latter indeed occurred in 2/25 bled animals in a previous study with survival up to 3 months[2]. The greater effect on skin would suggest that compensated oligaemia could also be associated with an increased incidence of wound dehiscence. This is merely further confirmation of the previous report of McGinn[1] that in both experimental animals and surgical patients blood loss insufficient to cause a fall in blood pressure was associated with

Table 1 *Wound break strength at 21 days, and fibroblast density, collagen packing and isotope uptake at 10 days (mean and s.e.m.) in healing rat laparotomy wounds from unbled animals and from animals bled 1 ml/100 g*

	Unbled	Bled
Skin break load (g/cm)	815 (61)	518 (66)
Muscle break load (g/cm)	517 (28)	402 (26)
Fibroblast density (/10^4 μm^2)	38·2 (2·3)	37·0 (2·5)
Collagen packing (%)	47·4 (1·8)	37·6 (2·1)
[^{3}H]thymidine uptake (% fibroblasts)	15·8 (0·8)	15·3 (0·6)
[^{3}H]leucine uptake (counts/fibroblast)	8·8 (0·5)	8·3 (0·3)
[^{3}H]proline uptake (counts/fibroblast)	8·0 (0·4)	10·6 (0·4)

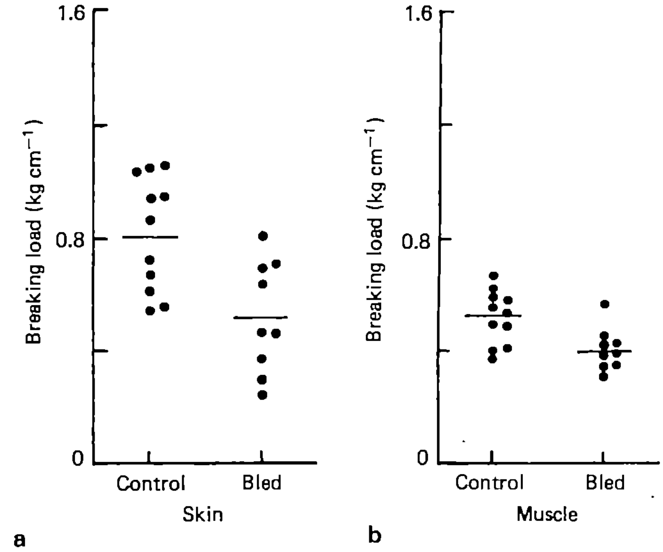

Figure 1 *Ultimate break strength (individual and mean) of skin (a) and muscle (b) layers of rate laporotomy wounds at 22 days in unbled animals (P<0·02) and in animals bled 1 ml/100 g (P<0·02). Both layers were significantly weaker in the bled animals than in the unbled control*

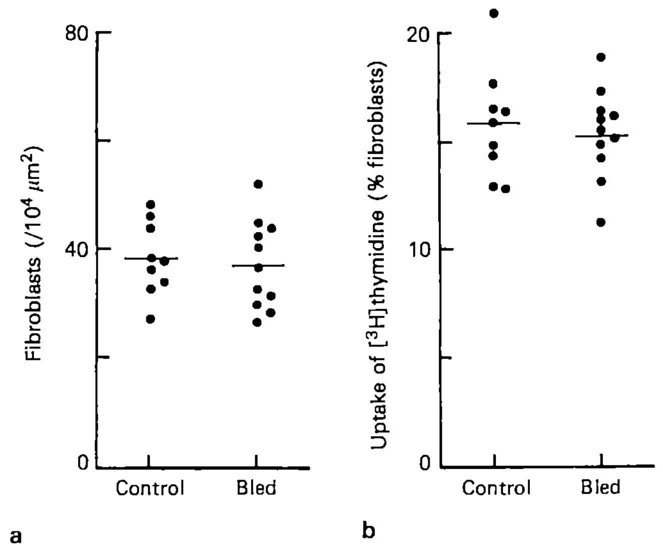

Figure 2 *Fibroblast density (a) and proportion of fibroblast nuclei taking up [^{3}H]thymidine (b) in healing zone of rat laparotomy wounds at 10 days (individual and mean), in unbled animals and in animals bled 1 ml/100 g. There were no significant differences between bled and unbled animals*

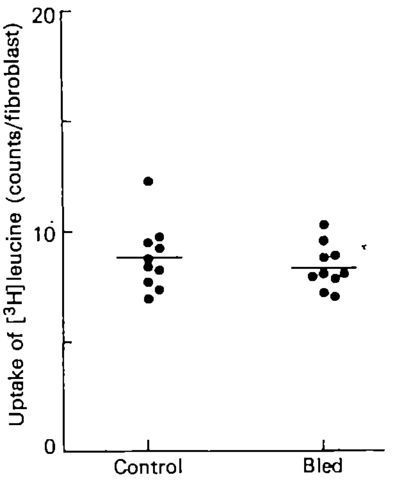

Figure 3 *Uptake of [^3H]leucine by fibroblasts in the healing zone of rat laparotomy wounds at 10 days (individual and mean), in unbled animals and in animals bled 1 ml/100 g. There was no significant difference between the unbled and the bled animals*

an increased incidence of wound dehiscence and incisional hernia. The possible mechanism leading to the impaired wound healing is of more fundamental importance both in understanding some of the basic factors in wound healing and in devising possible therapies for patients at risk.

Fibroblast function is highly susceptible to changes in oxygen tension[3,4] with total inhibition occurring below a P_{O_2} of 1·3 kPa. It has been demonstrated that blood loss can be associated with a reduced P_{O_2} in the region of wounds[5], whether the cardiovascular status is compensated oligaemia[6] or oligaemic shock[7]. Such hypoxia is more marked in skin and subcutaneous tissue than in the underlying muscle. It is, therefore, possible that tissue hypoxia is the precipitating factor; but the time lag observed in the healing process both with vascular anastomoses[8] and with laparotomy[2] make it likely that the transient hypoxia merely triggers longer term changes in collagen organization and turnover.

Although a reduction in DNA has been demonstrated in fibroblasts from healing wounds of bled animals at 6 days, this had returned to control wound values by 10 days[5]. This would be consistent with our previous findings at 6 weeks, and present results at 10 and 22 days, of no difference in fibroblast numbers or [^{3}H]thymidine uptake between bled and control animals. Equally, the present studies showed no impairment of general protein synthesis by fibroblasts in the healing area as assessed by [^{3}H]leucine uptake. We are, therefore, left with a specific defect in collagen metabolism as the cause of the impaired wound healing in bled animals. The present findings of increased [^{3}H]proline uptake by fibroblasts together with a reduced collagen density would be consistent with an increase in both the synthesis and reabsorption of collagen and/or tropocollagen, with the rate of reabsorption exceeding that of synthesis. It is well established that collagenase activity is increased in the region of healing wounds[3,9]. At colonic anastomoses the increased collagenase is also associated with an increased rate of turnover of type III collagen at 4 days after surgery[10]. These and the present findings would be in agreement with the theory that collagen is controlled principally by modulation of the rate of reabsorption of tropocollagen by the fibroblast[11]. Preliminary studies would suggest that the defect in collagen turnover following oligaemia is accompanied by a delay in change over from type I to type III collagen in the wound[12]. The extent to which variation in collagenase activity contributes to the observed differences between unbled and bled animals in this study cannot be determined; further studies are required on this aspect.

The current findings of a specific defect in collagen turnover accompanying compensated oligaemia, resulting in a shift to the right of the healing curve, has implications for surgical management. There would appear to be a strong indication in patients who have suffered blood loss without rapid, adequate replacement to use an absorbable suture with a relatively long time course of strength loss, such as polydioxanone, or bulk suture with a nonabsorbable monofilament, such as nylon, for anastamoses and wound closure.

With the positive findings in this study a more complete picture is being obtained by investigations of the complimentary parameters at the two time intervals of this study, and of both wound strength and fibroblast function at other time intervals after surgery.

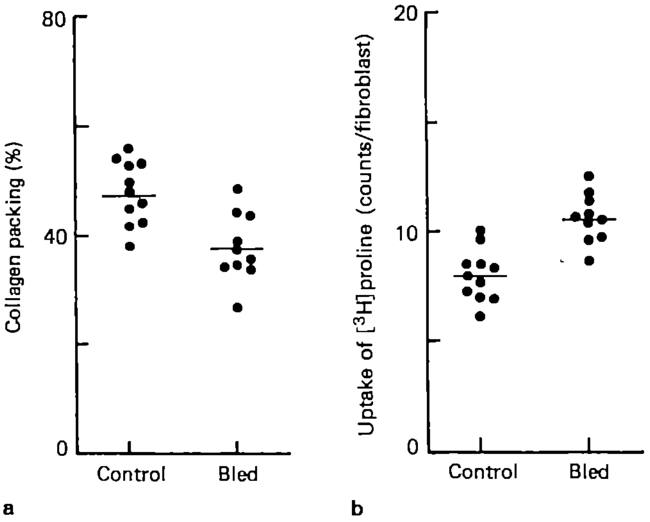

Figure 4 *Collagen packing density* (**a**), $P<0{\cdot}02$ *and uptake of* [^3H]*proline by fibroblasts* (**b**), $P<0{\cdot}01$ *in the healing zone of rat laparotomy wounds at 10 days (individual and mean), in unbled animals and in animals bled 1 ml/100 g. The amount of collagen was significantly less, but the* [^3H]*proline uptake significantly more, in bled than in unbled animals*

Acknowledgements

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Surgical workshop

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Use of orthopaedic staples to control aortic bleeding

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Occasionally, massive abdominal aortic haemorrhage occurs in a patient in whom it is inappropriate to use a prosthesis. This situation is most often when an infected aortic graft has ruptured intraperitoneally or has fistulated into the bowel. In these situations it is necessary to remove the graft and difficulty may be encountered controlling the haemorrhage from the divided aorta as dense adhesions may prevent a clamp being applied to the aortic stump, whilst sutures pull-out from the friable infected tissue.

An alternative approach to this problem is to place an orthopaedic staple across the aortic stump and hammer it into the vertebral bodies. Vitallium staples are available in a variety of sizes. The 16 or 22 mm size with 19 or 21 mm legs is the most appropriate. Too narrow a staple may tear into the side of the aorta as it is compressed against the vertebral body. The staples are held by a Blount staple holder (*Figure 1*). The staple is placed astride the aorta immediately proximal to the defect and hammered into position.

I have found this technique of value on several occasions when having to remove a ruptured and infected aortofemoral graft. In one instance, an aortofemoral graft had become infected and fistulated into the adjacent jejunum; the end-to-side graft was removed and both proximal and retrograde flow was controlled by staples (*Figure 2*). Circulation to the extremities can usually be maintained by an extra-anatomical bypass through an uninfected route.

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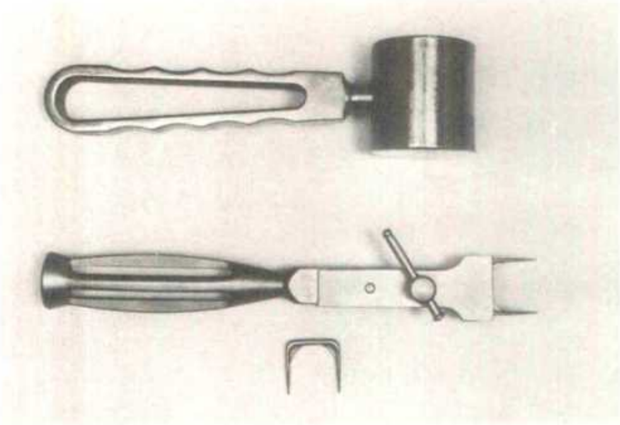

Figure 1 *A standard orthopaedic staple, the Blount staple holder with staple fitted and hammer*

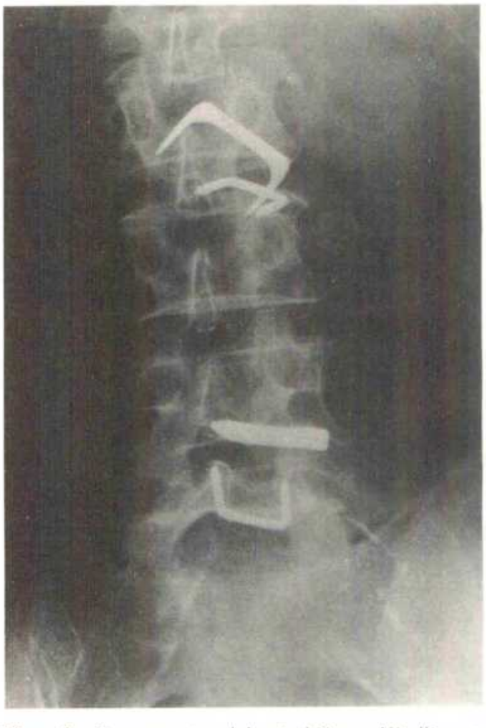

Figure 2 *Postoperative abdominal X-ray. Vitallium staples were used to control the proximal and distal aorta following removal of an aortic graft–enteric fistula*

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320–323

Improved wound healing response in surgical patients receiving intravenous nutrition

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The wound healing response was assessed in 90 surgical patients by measuring the accumulation of hydroxypyroline that occurred over a 7 day period, in fine tubes of thin walled GORE-TEX placed in the subcutaneous layers of the arm. In 47 patients presenting for intravenous nutrition, the wound healing response was less (0·34±0·23 µg hydroxyproline/cm of tubing) than that of 36 normally nourished patients (0·49±0·30 µg/cm; P<0·01*). However, it was higher when measured after intravenous feeding had commenced (0·88±0·62 µg/cm;* P<0·005*). In 29 patients two sequential studies of wound healing were conducted over a 14-day period of intravenous nutrition. The mean accumulation of hydroxyproline during the first week of intravenous nutrition was 0·36±0·24 µg/cm and this was increased significantly over the second week of feeding to 0·78±0·67 µg/cm;* P<0·005*. The wound healing response that occurred in wounds made after a period of pre-operative nutrition was better than that which occurred when only postoperative nutrition had been given (*P<0·02*). These results show that the wound healing response in surgical patients requiring intravenous nutrition is improved by this treatment. This improvement is seen after only one week of therapy and before there is an obvious change in nutritional status. It also appears that the improved wound healing response is more marked when intravenous nutrition is given before, rather than after the surgical procedure.*

Keywords: Wound healing, intravenous nutrition

For many years surgeons have known that prolonged septic starvation is associated with unhealed wounds, failure of fistulae to close and ununited fractures[1]. It is also known that nutritional repletion accompanied by weight gain and positive nitrogen balance usually results in a marked improvement. In spite of these observations, it has been difficult to supply scientifically evaluable data on wound healing in human subjects sufficient to satisfy those who maintain that intravenous nutrition (IVN) is not often effective. Here, using a new miniature technique[2], we present objective evidence which suggests that IVN effectively enhances the wound healing response in surgical patients.

Patients and methods

From June 1982 to August 1983, adult general surgical patients admitted to the wards of the University Department of Surgery, Auckland, New Zealand, were invited to participate in a study of wound healing. Patients were included in the present study if they fell into either of the following categories.

Normally nourished group. This group comprised patients who were normal anthropometrically and gave no history of recent weight loss or change in dietary intake.

Intravenous nutrition (IVN) group. This group comprised patients who had been referred to the University Department of Surgery for treatment that included intravenous nutrition.

Nutritional assessment

Each patient underwent a nutritional assessment which included a full medical and dietary history, a physical examination and anthropometric measurements. The latter included measurements of height, weight, mid-arm circumference and skinfold thickness[3]. Each patient was asked to recall his well weight and the physical examination was used to confirm the diagnosis and follow the clinical course.

The day before the wounding study, each patient had blood drawn for measurement of haemoglobin, white cell count and plasma albumin (SMA multichannel analyser), transferrin and pre-albumin (laser nephelometer, using Geringwerke transferrin and DAKO pre-albumin antisera).

Intravenous nutrition

This was administered through a central venous catheter according to the protocol we have detailed elsewhere[4,5]. The solutions comprised 50 per cent dextrose, 4·5 per cent crystalline amino acids, electrolytes, vitamins and a trace metal solution containing zinc, copper, manganese, chromium, iodine and selenium. Fat solution (1000 ml 10 per cent intralipid) was administered weekly. The average energy and nitrogen intake for the entire group was 42·8±6·9 kcal (180±29 kJ)/kg daily and 285±33 mg N/kg daily respectively.

Wound healing response

The method used to measure the wound healing response was previously described by Goodson and Hunt[2]. This involved the subcutaneous implantation of thin-walled GORE-TEX* tubes (1 mm diameter) along the line of a standardized needle track wound on the lateral aspect of the upper arm. The implants remained *in situ* for 7 days before extraction. An attempt was made to make two wounds of similar lengths (5–7 cm). The wound healing response was assessed from the amount of hydroxyproline in the implants at the end of the implantation period.

If the implant was inserted at the time of surgery then it was inserted while the patient was undergoing a general anaesthetic, if the implant was inserted at a time unrelated to surgery, the procedure was performed under local anaesthetic with two very small intradermal blebs being raised only at the entrance and exit points of the wounding needle. Each patient in the normally nourished group had a wound study begun at the time of surgery. The implant was removed 7 days postoperatively.

Each patient in the IVN group had at least one or more wound healing studies performed. No wound was within 3 cm of a previous wound. Because of the differing clinical courses of this heterogeneous

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* *Trademark of W. L. Gore & Associates, Inc.*

Table 1 *Wound healing in 36 surgical patients who were normally nourished and 54 patients who were fed intravenously*

	Normally nourished patients	Patients who received IVN	
		Group 1: wounds made just before starting IVN	Group 2: wounds made after a median of 11 days of IVN
Number of wound studies	36	47	72
Accumulation of hydroxyproline over 7 days (μg/cm of tubing) (mean ± s.d.)	0·49 ± 0·30	0·34 ± 0·23	0·88 ± 0·62

Normals *versus* group 1, $P < 0{\cdot}01$; normals *versus* group 2, $P < 0{\cdot}001$; group 1 *versus* group 2, $P < 0{\cdot}00001$

Table 2 *Anthropometric measurements, plasma proteins and haematology: results of two wound healing studies in 29 surgical patients receiving IVN*

	Wound made at start of IVN (wound 1)		Wound made after 7 days of IVN (wound 2)		*P*
Anthropometry					
Weight (kg)	58·3 ± 12·9	(29)	58·9 ± 13·3	(29)	n.s.
Body mass index (kg/m^2)	21·5 ± 3·6	(29)	21·7 ± 3·7	(29)	n.s.
Biceps skinfold (mm)	5·0 ± 2·7	(29)	4·9 ± 2·3	(29)	n.s.
Triceps skinfold (mm)	11·2 ± 6·0	(29)	10·9 ± 5·2	(29)	n.s.
Subscapular skinfold (mm)	10·0 ± 4·9	(28)	10·0 ± 5·1	(29)	n.s.
Mid-arm circumference (mm)	255 ± 35	(29)	257 ± 35	(29)	n.s.
Blood tests					
Albumin (g/l)	31·6 ± 6·0	(29)	33·6 ± 4·2	(28)	n.s.
Pre-albumin (mg/100 ml)	14·6 ± 8·4	(25)	30·1 ± 9·4	(27)	n.s.
Transferrin (mg/100 ml)	184 ± 74	(24)	209 ± 74	(27)	n.s.
Haemoglobin (g/l)	113 ± 27	(28)	114 ± 20	(24)	n.s.
Lymphocyte count ($\times 10^9$/l)	1·3 ± 0·7	(27)	1·6 ± 0·8	(23)	n.s.
Wound healing					
Accumulation of hydroxyproline over 7 days (μg/cm of tubing)	0·36 ± 0·24		0·78 ± 0·67		< 0·005

Values are mean ± s.d.; values in parentheses are numbers of patients

group of patients it was necessary arbitrarily to decide on suitable times to study each patient on the day of starting their course of IVN (day 0) and then again after the completion of 7 days of IVN. If a patient in this group underwent surgery then a wound study was performed at the time of surgery. If a patient remained on IVN for some time then an attempt to study these patients at weekly intervals was made. On the seventh post-wounding day, without any anaesthesia, the GORE-TEX implants were pulled out of the wound, the length of only the subcutaneous portion was measured, and this part of the tube was cut up into small pieces and placed in vials. One millilitre of distilled water was introduced into the vials and allowed to remain for a period of half an hour while the vial was placed in a water bath at 37°C. This procedure was repeated after the first rinse had been aspirated in an effort to remove all soluble material. Each vial was then freeze dried and sealed for hydrolysis with 1 ml 6M HCl. After hydrolysis for 18 h at 100°C the tubes were unsealed, evaporated to dryness and the deposit resuspended in 1 ml water. Duplicate aliquots of this were taken out for hydroxyproline analysis using the chloramine T/4-(dimethylamino)-benzaldehyde reaction[6]. The resultant colour was read on a spectrophotometer set at 550 nm and the results expressed as micrograms of hydroxyproline/cm of GORE-TEX.

Statistical analysis

Student's test, paired (*Table 2*) and unpaired (*Tables 1* and *3*) as appropriate, was used according to variance equivalence. In non-normally distributed data a Wilcoxon two sample test was used.

Results

Overall results

Thirty-six normally nourished patients had a total of 36 wound healing studies and 54 patients who received IVN had a total of 119 wound healing studies. In *Table 1*, the 119 wound healing studies carried out on the 54 IVN patients have been divided into two groups. Group 1 represents all the wound studies that were begun on the day of commencement of IVN; group 2 represents the results of all the wound studies that were initiated after the IVN had been recommenced (median, 11 days; range 3–116 days). It is clear that the mean hydroxyproline accumulation into the GORE-TEX tubes which were inserted at the start of the course of IVN (group 1) was significantly less than that which accumulated into the tubes of the normally nourished patient group and very significantly lower than the wound studies which were made after IVN had commenced. The results from the studies performed after IVN had commenced (group 2) were significantly higher than those from the normally nourished group.

Prewounding versus *postwounding IVN*

Of the 54 patients studied while being treated with IVN, 29 had their initial wound study begun on day 0 of the course, with a second study begun after the completion of 7 days of IVN. *Table 2* shows that the mean accumulation of hydroxyproline in the GORE-TEX tubes in wound 1 was 0·36 ± 0·24 μg/cm and it was 0·78 ± 0·67 μg/cm in wound 2 ($P < 0{\cdot}005$). *Table 2* also shows that there was no change in the anthropometric measurements, the plasma proteins or the haematological markers between the two wound studies.

Pre-operative versus *postoperative IVN*

Of the 54 IVN patients studied, 18 underwent a total of 19 surgical procedures. Each of the 18 patients had a wound study begun at the time of their surgery making a total of 19 wound studies. Ten of these studies occurred in patients who had not received any IVN pre-operatively, whereas nine occurred in patients who had received pre-operative and postoperative IVN (median 14 days; range 7–74 days). *Table 3* gives the relevant

Table 3 *Indices of nutritional state and wound healing response in 10 patients who received postoperative IVN compared with those in nine patients who received pre- and postoperative IVN*

	Postoperative IVN (10 wounds studied)	Pre- and postoperative IVN (9 wounds studied)	*P*
Age (years)	59·4 ± 15·2 (10)	55·2 ± 13·8 (9)	n.s.
Men:women	6:4	3:6	
Anthropometry			
Weight (kg)	55·5 ± 11·7 (10)	50·9 ± 11·9 (9)	n.s.
Weight loss (%)	20·7 ± 7·9 (10)	22·0 ± 12·4 (9)	n.s.
Body mass index (kg/m^2)	19·4 ± 3·0 (10)	18·9 ± 4·6 (9)	n.s.
Biceps skinfold (mm)	3·4 ± 1·7 (10)	4·8 ± 2·9 (9)	n.s.
Triceps skinfold (mm)	7·8 ± 6·0 (10)	9·7 ± 4·3 (9)	n.s.
Subscapular skinfold (mm)	8·3 ± 5·2 (10)	7·1 ± 3·1 (9)	n.s.
Mid-arm circumference (mm)	237 ± 29·6 (10)	236 ± 41·6 (9)	n.s.
Blood results			
Albumin (g/l)	33·0 ± 6·6 (10)	33·1 ± 9·0 (9)	n.s.
Pre-albumin (mg/100 ml)	18·1 ± 11·6 (9)	18·5 ± 8·8 (7)	n.s.
Transferrin (mg/100 ml)	226 ± 81·3 (9)	215 ± 81·0 (7)	n.s.
Haemoglobin (g/l)	122 ± 14·9 (10)	115 ± 22·4 (8)	n.s.
Lymphocyte count ($\times 10^9$/l)	1·3 ± 0·45 (9)	1·6 ± 1·1 (8)	n.s.
Wound healing			
Hydroxyproline content (μg/cm of tubing)	0·33 ± 0·20 (10)	0·69 ± 0·37 (9)	< 0·02

Values are mean ± s.d.; values in parentheses are numbers of patients

patient information for each of these two groups obtained from an assessment just before surgery. It is clear that there is no significant difference between the two groups for any of the measured indices of nutritional state. However, the wound healing response results, also shown in *Table 3*, demonstrate that the group receiving pre-operative and postoperative IVN had significantly higher accumulation of hydroxyproline in their tubes than the group receiving postoperative feeding only.

Discussion

We present here objective evidence that the wound healing response in surgical patients requiring IVN is improved by this treatment. This improvement is seen after only one week of nutritional therapy, and before recognized indices of nutritional status are significantly changed. Furthermore, it appears that the improvement in the wound healing response is more marked when IVN is given before, rather than after the surgical procedure. Although the major reason for studying the 36 normally nourished patients was to provide a reference mark against which to judge the wound healing response of the IVN patients, and its change with therapy, it is interesting to note that the GORE-TEX tubes in the wounds made in patients during their treatment with IVN accumulated more hydroxyproline than those of the normally nourished patients. However, it may be relevant to point out that the wound healing studies in the normally nourished patients, through necessity, were begun at surgery and therefore most of these patients underwent a period of peri-operative starvation. It is possible that either the surgery itself, or the period of starvation surrounding it, may depress the wound healing response from that which is truly normal.

Although it is clear that this new technique which we have used to measure the wound healing response is a major advance for clinical research, there are as yet a number of limitations as to its use which have been discussed in detail elsewhere[7]. Apart from the variability of the results both between patients and even for a single patient, there is the difficulty of ascertaining the meaning of the changes in biological terms. It may be incorrect to class this response as solely one of wound healing, as the presence of collagen in these tubes depends on a complex cascade of biological events. These begin with acute inflammation and cellular invasion, macrophage stimulation, fibroplasia and then the final step of collagen production[8]. Histological studies in rats[9] suggest that in protein energy depletion there is a lack of cellular invasion into the tubing which is corrected by refeeding. This underlines the fact that this technique is measuring more than just the wound healing response as a deficiency in acute inflammation, and cellular invasion has widespread implications for host defence.

Although the clinical study by Collins *et al.*[10] suggested that postoperative IVN was associated with better healing in perineal wounds after rectal excision, until now there have been few data which confirm unequivocally the clinical impression that IVN has an effect on the wound healing in surgical patients.

Our data suggest that IVN does have a positive effect on the wound healing response in man and that this improvement occurs over quite a short period. Clearly more and better studies need to be undertaken and formal prospective studies are awaited. Until then the surgeon can feel more assured that IVN does help his malnourished patient to heal more effectively and that a short period of pre-operative and postoperative nutrition may be of real benefit to some carefully selected patients.

Acknowledgements

We would like to acknowledge Dr Goodson and Dr Hunt for their advice on setting up this technique in our laboratory, W. L. Gore and Associates for providing the GORE-TEX tubing, and to Mr M. H. Flint and the connective tissue research group for their help in the analysis of the samples.

D. A. Haydock is a Medical Research Council of New Zealand Training Fellow.

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Suction curette in the management of hydatid cysts

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Whilst hydatid cyst (*Echinococcus granulosus*) is uncommon in the United Kingdom it is endemic in many areas of the world including Mediterranean countries, parts of Africa, the Middle East, Asia, China and South America. Despite the advancing role of chemotherapy[1] most patients will undergo operation and recurrence is one of the principal postoperative problems, occurring in approximately 10 per cent of patients[2]. Spillage of viable hydatid protoscoleces during operation is one of the important causes of recurrence. The most widely used technique to try to reduce this risk is to inject scolicidal agents into the cyst before opening to achieve the conservative cystectomy operation with preservation of at least part of the ectocyst.

Scolicidal agents are not without hazard. Acute, sometimes fatal, toxicity from formalin has been described[3]; sclerosing cholangitis may occur if the fluid leaks into the biliary tree and has been described following the use of formalin, ethanol and hypertonic saline[4]. Sclerosing cholangitis in hydatid disease has not been described before operation although biliary obstruction due to intraluminal debris (daughter cysts/laminated layer) or compression by the cyst are common. The injection of scolicidal agents into a cyst where biliary communication is demonstrated or suspected is probably now an unacceptable risk. Chemotherapy may have a role in the perioperative setting; short courses of albendazole following peritoneal innoculation in the gerbil produce a significant reduction in the number of cysts which develop[5] and pre-operative therapy of 1 month or more in man almost always produces non-viable cysts.

Experienced surgeons have developed special devices to try to limit spillage, a metal cone may be either frozen or sucked on to the liver surface and the cyst opened through this, thus limiting spillage[6]. These devices are clumsy, often require a modified surgical approach and are unlikely to be available to other than very specialized surgeons. There are no data to suggest that they have reduced postoperative recurrence rates.

Why does spillage occur? Viable cysts are usually under considerable tension and fluid escapes under pressure when the cyst is aspirated or incised. Conventional sucker devices are inadequate for emptying the cyst contents which often include large segments of laminated membrane (part of the cyst wall) and many daughter cysts; the sucker blocks and spillage occurs.

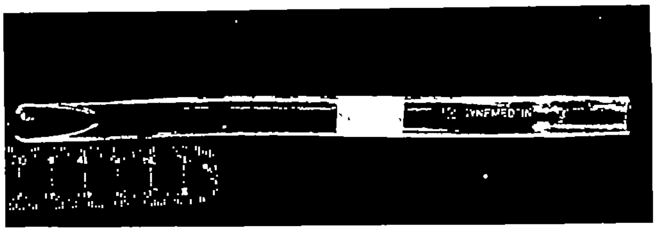

Figure 1 *Large diameter suction curette*

During the last 3 years we have used a large diameter suction curette (*Figure 1*). This device is usually used by gynaecologists for suction termination of pregnancy. The curette is available in various sizes and a large (12 mm) curette has been found most useful. This instrument has not ever blocked in 16 cases and removes the contents of the cyst rapidly. No damage to the pericyst cavity was produced by the curette.

The use of this suction curette does not remove the need for packing off the surgical field with swabs soaked in a scolicidal agent (0·5 per cent silver nitrate is effective and is probably less toxic than others[7]) and if no biliary communication exists then the ectocyst cavity can be cleaned with similar swabs.

The suction curette device is inexpensive, widely available and may be of use to surgeons faced or surprised by a hydatid cyst.

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324–326

Major hepatic resection for colorectal liver metastases

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A 6½ year experience in the management of hepatic colorectal metastases in a specialist unit is reviewed. During the period studied, 48 patients were referred of whom only 24 actually came to resection. There were two in-hospital deaths, at 20 and 60 days, and six patients had non-fatal complications. Although the extent of resection was greater than in most reported series (13 right hepatectomies and 6 extended right hepatectomies), the results of resection were broadly the same as those of others, with a median survival of 30 months and 2 and 3 year survivals of 50 and 44 per cent respectively. A number of factors which others have considered to be of prognostic significance were examined. Tumour clearance was the only important prognostic indicator, where a 5 mm clear margin between the tumour and cut surface produced a significant difference in survival. It is suggested that a much larger number of patients in the UK with hepatic colorectal metastases might be considered for resection.

Keywords: Colorectal carcinoma, liver metastasis

According to the Office of Population Censuses and Surveys[1], in 1981 some 16 500 people in England and Wales died from carcinoma of the colon and rectum. This represents an incidence of 20–30 000 new cases per annum and is similar to that of other Western populations[2]. At death, hepatic involvement is present in 40–70 per cent of cases[3,4], and a quarter of those undergoing laparotomy for colorectal cancer have synchronous hepatic metastases[5]. Most liver metastases are not amenable to resection because of factors related to age and fitness of the patient[6] or to the extent of tumour spread[7]; however, if 5 per cent of all colorectal hepatic metastases were amenable to resection then several hundred cases each year in England and Wales might benefit from the procedure. Despite this, the number of resections being undertaken in the UK and in other countries remains small.

That large hepatic resections for tumour can be performed with acceptably low morbidity and mortality is no longer in question[8–11]. It remains controversial whether or not resection of lesions is justified in terms of duration and quality of survival. The purpose of this paper is to present the clinical data and outcome of hepatic resection for colorectal metastases in this unit and examine factors which may be of prognostic value.

Patients and methods

From July 1979 to February 1986, 48 patients with colorectal hepatic metastases were referred to the hepatobiliary surgical unit at the Royal Postgraduate Medical School, Hammersmith Hospital, specifically for resection of their liver tumours. Only 24 patients actually came to resection. Fourteen patients were excluded because of disseminated disease (detected by computed tomography (CT) in eight, bone scan in three, chest radiography in two and angiography in one) and did not undergo laparotomy or laparoscopy. Eight patients were excluded at laparotomy or laparoscopy because they were found to have more widespread disease than had previously been anticipated. The remaining two patients declined surgery.

The patients who underwent surgery consisted of 15 men and 9 women, whose ages ranged from 22 to 69 years (median 53 years). An equal number of patients had synchronous and metachronous metastases. In the metachronous group, the median interval between primary resection and the diagnosis of metastasis was 13 months (range 4–48 months). Metastases were detected by elevation in the serum carcino-embryonic antigen level in eight; a further three were investigated by CT, ultrasound or radioisotope scan of the liver because of abdominal symptoms; the remaining patient was found to have a liver deposit at the time of a 'second look' laparotomy for a colonic suture line recurrence.

The primary tumours were all adenocarcinomas and were located in the rectosigmoid in 21 patients, the ascending colon in 2 and the transverse in 1. The local staging of the tumours according to Dukes' classification was: stage A in 1 patient, B in 13 and C in 10.

The metastases were solitary in 16 cases, 2 deposits were present in 7 patients, and 1 had multiple unilobar deposits. The size of the deposits varied from 5 mm to 15 cm (median 5 cm) but there were six tumours greater than 10 cm in diameter. Nineteen patients had metastases confined to the anatomical right lobe, two had right and left lobe deposits, while in three the left lateral segment only was involved. In those patients with synchronous metastases, none underwent simultaneous bowel and liver surgery. The median interval between the two operations was 3 months (range 1–7 months), after which time further investigations were undertaken to exclude dissemination or colonic recurrence, before hepatic resection.

Nineteen right hepatic resections were carried out including six extended resections. Three patients underwent left lateral segmentectomies and two others had other segmental resections. One of the two patients in whom a segmentectomy was carried out was found at laparotomy to have tumour extending from the right lobe of the liver along the lesser omentum into the pylorus. The entire tumour mass was resected *en-bloc*. Six patients had subcapsular metastases abutting on and apparently invading the diaphragm and in these cases the resection included the affected portion of diaphragm.

There were no intra-operative deaths, but two patients died in hospital. One died on the 20th day after an uneventful postoperative course: at autopsy portal vein thrombosis was found, probably associated with temporary clamping during parenchymal dissection. The second died on the 60th day of renal and hepatic failure. This patient had undergone arterial embolization 3 days before resection, which rendered the procedure difficult due to major collateral formation.

Six patients had serious non-fatal complications; three required re-operation in the immediate postoperative period; two because of haemorrhage and one because of portal vein thrombosis, which was successfully treated by thrombectomy. Later complications consisted of three subphrenic abscesses which were managed by percutaneous drainage.

Actuarial survival statistics were calculated by life table analysis using the Survival procedure of the computer program SPSS (Statistical Package for the Social Sciences, McGraw-Hill).

Results

The survival of all patients is shown in *Figure 1*. Ten patients have died between 20 days and 37 months. Eight of these died

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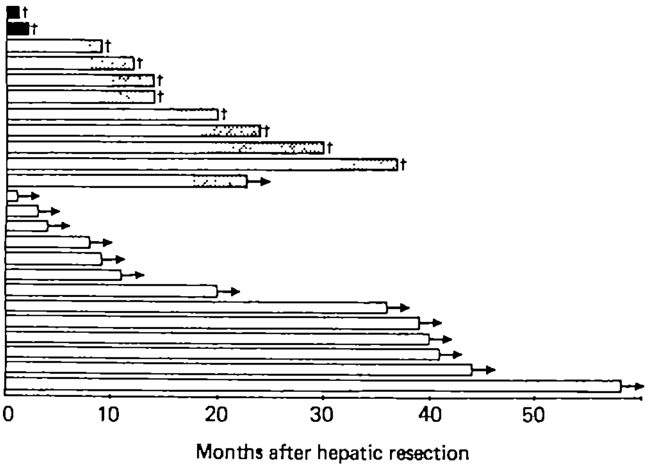

Figure 1 *Follow-up survival histogram for 24 patients who underwent resection of their metastases.* †, *Dead:* →, *alive:* ■, *in hospital deaths (20 and 60 days);* □, *recurrence*

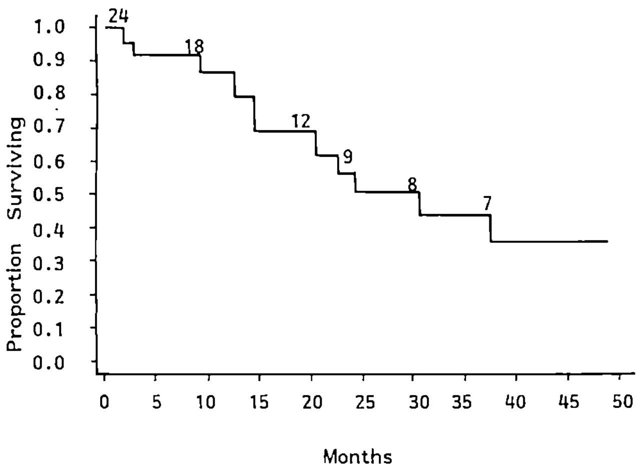

Figure 2 *Actuarial survival curve for all 24 patients*

from tumour recurrence, of whom three had recurrence in the liver and five had extrahepatic recurrence. All patients with hepatic recurrence had a tumour-free margin less than 5 mm in the resection specimen. The median time period from resection to the diagnosis of recurrence was 17 months (range 10–32 months), and the median length of survival following the diagnosis of recurrence was 4 months (range 1–12 months). One patient remains alive with known extrahepatic recurrence at 24 months, while the remaining 13 patients are alive with no evidence of recurrence with a follow up of 1–58 months.

Thirteen subcapsular metastases were examined for microscopic evidence of capsular invasion by tumour; in none was it present. Furthermore the six juxta-diaphragmatic tumours were shown to have evidence of inflammatory changes only with no tumour invasion of the diaphragm or Glisson's capsule.

Life table analysis (*Figure 2*) reveals an actuarial median survival of 30 months with 2 and 3 year survival rates of 50 and 44 per cent respectively. Those patients who had complete clearance of their metastases had a longer survival than patients who had less than 5 mm of uninvolved liver between the tumour and the resection line (*Figure 3*): all 14 of the former were alive at 1 year, compared with only 1 in 4 in the latter group ($P = 0{\cdot}003$, Fisher's exact test).

Discussion

Patients may not be considered for resection of colorectal liver metastases because the surgeon is unaware that the metastases exist or because he considers that resection is not worthwhile. In the case of synchronous lesions some studies[12,13] have shown that the surgeon's intra-operative assessment of the liver is a reliable indicator of the presence of a deposit. A study by Goligher[14] demonstrated that in a series of nearly 900 patients, there was an 11·5 per cent incidence of synchronous tumours, but in a group of patients who died unexpectedly soon after surgery where the liver was thought to be free from tumour, approximately 16 per cent were found at autopsy to have liver metastases, thereby increasing the incidence of synchronous disease to approximately 26 per cent.

The use of low abdominal incisions in most of these cases made the careful palpation of the entire liver difficult, which may explain the difference between the laparotomy and post mortem incidence of synchronous metastasis. This study predates the wide use and availability of liver scanning methods for pre-operative screening of such patients. Another study[5] showed an incidence of synchronous tumours of 24·5 per cent. Metachronous tumours will be apparent within 2 years of resection of the primary disease in approximately 50 per cent of all patients who develop hepatic metastases[3]. Undoubtedly many of the early metachronous tumours are, in fact, missed synchronous lesions which could not be palpated at laparotomy.

Pain is an infrequent early symptom and may only occur if necrosis with haemorrhage into the metastasis causes tension in Glisson's capsule. Anorexia and weight loss are similarly not early features of hepatic metastasis. Ascites may occur not only with peritoneal tumour involvement but also with post-sinusoidal hepatic venous obstruction. Hepatomegaly and jaundice are late signs. By the time clinical manifestations of metastasis are present, the disease is likely to be so advanced as to preclude excision. Elevation of alkaline phosphatase, lactate dehydrogenase and transaminases may be earlier indicators of the presence of metastases but these are neither specific nor sensitive enough to provide reliable information on their own.

Carcino-embryonic antigen (CEA) is the best single laboratory test for detecting hepatic metastatic disease in patients with colorectal cancer[15,16]. An elevated CEA was the means of detecting 66 per cent of metachronous tumours in our series. Imaging techniques such as CT, ultrasound or technetium-99m sulphur colloid scintiscan may improve the overall detection rate for liver metastases. In particular CT scanning used together with CEA and routine liver function tests provide the best means of screening the liver for metastases[16]. The combined laboratory and imaging tests still only provide an accuracy of 76 per cent[16] so that patients who are thought not to have a metastasis at the first testing should be re-investigated at regular intervals. Ultrasonography and CT scanning were responsible for detecting metachronous lesions in 25 per cent of our patients.

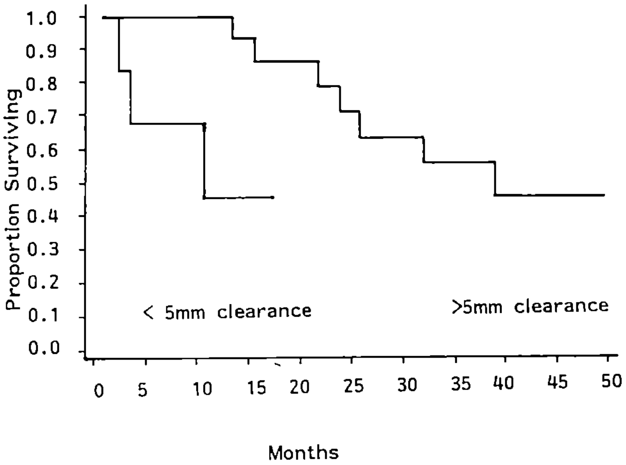

Figure 3 *Actuarial survival curves for patients with and without complete metastatic clearance at resection*

Small, solitary lesions mostly requiring no more than a wedge excision have been shown to warrant removal[17] but only approximately 25 per cent of colorectal liver metastases are solitary or unilobar.

The role of major resection for colorectal metastases remains a subject of debate. Although numerous studies have suggested that major resection may be valuable[8–10,17], there are no randomized prospective trials comparing resection with no resection. A comprehensive retrospective study of unresected patients has been made using historical controls in whom the selection criteria for resection were matched[18]. It was found that patients with resectable but unresected hepatic metastases had median survivals of 24 and 18 months for solitary and multiple unilobar lesions respectively and 20 per cent of patients who were not resected lived for 3 years. However, beyond 2–3 year survival, differences in favour of resection of certain lesions have been noted[19]. Some 42 per cent of patients survived 5 years or more after resection of apparently solitary metastases and 28 per cent lived for 10 years or more in this group[8]. In a later study[18], the same group showed a 37 per cent 5 year survival following resection for metachronous, large (> 4 cm), multiple lesions. The number of metastases has been regarded as being an important determinant of survival by some workers[9,20] while others have attempted to stage the disease and correlate this with outcome[21].

A recent multicentre study[22] regarding the patterns of disease recurrence after resection of colorectal cancer in 607 patients has shown that recurrent tumour occurred in the liver in 43 per cent and in the lung (with or without other organ involvement) in 31 per cent. A multivariate analysis showed that patients with histologically involved resection margins or bilobar metastases were at an increased risk of liver recurrence (68 and 44 per cent respectively). The 5 year survival for the entire group was 33 per cent and the 5 year disease-free survival was 25 per cent.

A major difference between the present series and those reported by some others[9,10,18,20,21] is the high proportion of large resections carried out. This is likely to be the result of the referral pattern to Hammersmith Hospital in that lesions which could be dealt with by lesser procedures might be operated on by the surgeons who diagnose their presence and only potentially extensive or complex resections were referred to this specialist unit. The extent of resection did not have any prognostic significance for our patients, nor indeed did the size, number or timing of appearance of the metastases. Similarly the Dukes' staging of the primary lesion had no influence on survival. In keeping with the findings of the multicentre study on the subject of tumour recurrence[22] we found that completeness of excision with a 5 mm disease-free margin had prognostic significance both in terms of hepatic recurrence and survival.

The finding that in our series subcapsular or juxta-diaphragmatic tumours showed no tumour invasion but only inflammatory changes is important[23], and is in keeping with earlier reports of the liver capsule's impermeability to tumour invasion[24,25]. Thus apparent diaphragmatic involvement on CT scanning or at laparotomy should not be regarded as a contraindication to attempted curative resection.

Surgical resection of colorectal metastases is acceptably safe when undertaken in a specialist centre. Resection improves survival certainly in solitary metastases and possibly in selected patients with unilobar multiple ones and, of course, offers the only hope of cure. The number of potential candidates in the UK for hepatic resection for metastases is likely to be in excess of 1500 per annum. This is in keeping with similar estimates from the United States[10]. Abandoning all hope for these patients is a misplaced sentiment.

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Paper accepted 16 October 1986

Vascular Surgical Society of Great Britain and Ireland

The following abstracts are from a selection of the papers presented at a meeting of The Vascular Surgical Society of Great Britain and Ireland, held at the Institute of Education, University of London on 12 and 13 November 1986. (President: Mr M. Birnstingl.)

Br. J. Surg. 1987, Vol. 74, April 327–332

Two year study of patency of a new 3·8 mm internal diameter polyetherurethane urea (Biomer) arterial prosthesis

Linda De Cossart, D. Annis and P.L. Harris, *Broadgreen and Royal Liverpool Hospitals, Liverpool, UK*

The performance of a new compliant microfibrous polyetherurethane urea (Biomer) synthetic artery of our design has been studied in a series of 26 consecutive implants as carotid artery replacements in dogs. A 4 cm length of carotid artery was excised and replaced by a similar length of the synthetic artery. All implants were performed by the same surgeon (L.De C.). Twelve interrupted sutures of 6/0 Prolene were used to fashion both end-to-end anastomoses.

Assessments of patency of the grafts were made using fortnightly Toshiba B scan ultrasound with linked Doppler shift waveform analysis.

Twenty-six grafts were implanted. Seventeen grafts have remained patent for periods > 24 months. Five failed acutely (within 2 weeks), four failed 59–201 days after operation. Sixteen of those grafts that remained patent for > 24 months have been removed for histopathological examination, which has demonstrated a limited extension of a new intima onto the inner surface of the grafts. The new intima is firmly attached and shows no sign of pseudo-intimal hyperplasia. The inner surface, uncovered by neointima, nevertheless, has extensive endothelial cover.

Of practical importance are the excellent handling qualities of the graft. It cuts cleanly without fraying and a stitch placed 1 mm from the cut end of the graft will hold securely. There is no needle hole bleeding.

The graft has both axial and circumferential compliance similar to that of the natural artery it replaces. The good 2-year patency reported here may stem from the haemodynamic advantage of matched compliance or, more simply, it may be that the match of mechanical properties has allowed us to unite a natural to a synthetic artery using the well established techniques which have evolved for the joining of natural arteries.

Expectations of PTFE in the severely ischaemic lower extremity

G. O'Leary, J.A. O'Donnell and L. Fitzgerald, *Department of Surgery, University College Cork, Cork, Ireland*

Reported benefits of polytetrafluoroethylene (PTFE) for lower extremity bypass have varied widely. Since 1979, we have used PTFE for lower extremity bypass when a suitable autogenous saphenous vein was unavailable. Operative indications have been conservative: rest pain or necrosis. Long-term results of PTFE use are needed to define more clearly its role in lower extremity bypass surgery, and demonstrate realistic expectations for PTFE patency and limb salvage in the severely ischaemic lower limb.

A total of 103 bypass procedures are presented which include 67 femoropopliteal (FP), and 36 femorotibial (FT) bypasses. Operative mortality and patient survival are presented. Bypass patency (per cent) and limb salvage (per cent) rates by the life table method have been plotted for the following sub-groups: FP above-knee (FPAK) and below-knee (FPBK), FT and PTFE with a distal arteriovenous fistula (FTAV).

Perioperative mortality was 2·2 per cent. Patient survival was 68 per cent at 5 years. Patency (per cent) at 5 years for FP, FPAK, FPBK, FT and FTAV was 47, 94, 39, 8 and 17 per cent respectively. Limb salvage for these groups was 79, 94, 74, 27 and 41 per cent respectively.

Both patency and salvage rates were so poor with more distal bypass procedures that an alternate approach was required. We now undertake *in situ* vein bypass, which reduces the requirement for distal PTFE procedures. In fact, we recommend elective amputation in preference to a distal bypass with PTFE, and only consider the use of PTFE distally when the patient is unwilling to consider elective amputation.

Comparison of prospective and retrospective data in a group of patients with PTFE femoropopliteal bypass grafts

M. Goldman and G. Kenchington, *Department of Surgery, University of Birmingham, Birmingham, UK*

Almost always the clinical performance of a particular vascular graft is based upon retrospective reviews. Surgeons assume that inconsistencies in the published literature reflect indefinable differences in local patient populations and clinical practice. This study examines the alternative possibility that the method of data collection is responsible.

From August 1980 to May 1982, 24 patients with PTFE femoropopliteal grafts were studied prospectively and the same patients should have appeared in a retrospective review undertaken by another researcher in 1985. Both studies had recorded the indications for surgery, arteriographic run-off, graft insertion, presence of four risk factors, and 1-year patency. The retrospective and prospective findings are compared.

The retrospective search failed to locate 3 (12·5 per cent) of the 24 patients studied prospectively. According to prospective data, 50 per cent of patients had rest pain, whereas retrospective data suggested it was 67 per cent. Although the mean number of run-off vessels in each group was similar at 2·3 ± 0·9 (mean ± s.d.) (prospective) and 2·5 ± 0·8 (retrospective) there was a disagreement between databases in 17 of 21 patients. In three patients (14 per cent) there was disagreement concerning the site of distal graft insertion. The risk factor profile concurred in only 15 of 21 patients. Patency at 1 year was 61·9 per cent (13 of 24) measured prospectively or 66·6 per cent (14 of 21) measured retrospectively. Overall, out of 192 pieces of information gathered prospectively, retrospective analysis showed 32 inconsistencies (17 per cent) and 24 facts (12·5 per cent) were lost.

Prospective and retrospective data on the same patients are different. Perhaps this explains the failure of clinical series to define the optimal prosthetic material.

Lower limb angioplasty: a review of 300 procedures

A. Howd, H. Loose, J. Chamberlain and G. Proud, *Departments of Surgery and Radiology, Freeman Hospital, Newcastle upon Tyne, UK*

Transluminal 'angioplasty' has become a widely used technique in vascular surgery in recent years. In this centre we have been using this technique since 1981, and now present the results of 300 procedures in lower limb vessels.

A total of 227 patients (169 men and 58 women) have undergone 300 transluminal procedures with a total of 360 lesions dilated. These include 211 iliac artery stenoses, 54 femoral artery stenoses, and 72 femoral artery occlusions. The overall technical success rate was 88 per cent with those that failed being mainly attempted dilatations of the femoral artery or distal vessels.

The 2-year cumulative patency rates are 83 per cent for iliac stenoses with good run-off; 61 per cent for iliac stenoses where the superficial femoral artery is occluded; and 64 per cent for short femoral artery stenoses and occlusions with good run-off. Dilatations of multiple femoral artery stenoses, long occlusions, and femoral arteries with poor run-off did not do well with a 1-year patency of 31 per cent.

The complication rate was low with an incidence of minor complications of 10 per cent. These included rashes, haematomata, transient numbness and minor distal emboli. There were 12 serious complications (4 per cent) including 6 acute thromboses, 2 false aneurysms, 1 bleeding from the puncture site, 1 neurological deficit and 2 deaths from myocardial infarction.

Transluminal 'angioplasty' has now established a place in the treatment of patients with vascular disease and may be the preferred treatment for localized disease of the lower limb vessels.

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Predicting failure of femoropopliteal bypasses using ultrasonic flowmetry

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Although intra-operative flow measurements have long been used as predictors of patency in femoropopliteal bypass, such techniques have not effectively anticipated failure after the immediate postoperative period.

We have studied 85 femoropopliteal and femorotibial bypasses prospectively over a 12 month period with 6 monthly assessment consisting of a clinical evaluation, ankle pressure indices and blood flow volume measurements both at rest and following a standard hyperaemic test.

During the course of the study 14 bypasses occluded. In five cases the preceding assessment had been normal and occlusion had been sudden and unexpected. Of these five bypasses, four were synthetic grafts of the remaining nine occlusions (all saphenous vein grafts), eight had demonstrated suboptimal peak blood flow during reactive hyperaemia ($<$ 200 per cent of resting flow), and all six that had been studied at least twice showed a significant fall in resting blood flow and in post-hyperaemic blood flow and ankle pressure index. If saphenous grafts alone are considered ($n = 68$) then a failure to double the resting blood flow after reactive hyperaemia would have predicted eight of the ten failures, with a specificity of 90 per cent.

In a further five patients, failing grafts were identified by these criteria and were investigated by arteriography. In one case a refashioning of the distal anastomosis was successful, but in the other cases a combination of progressive disease, poor run-off or generalized bypass narrowing prevented salvage surgery.

Although certain bypass occlusions are not predictable, this study suggests that there is a group of patent but haemodynamically failed bypasses which are easily detected by ultrasonic flow measurement, and which, being in great danger of occlusion, warrant further investigation.

Intravenous digital subtraction angiography in the evaluation of vascular grafts

F.M. Ameli, E.L.St. Louis, J.L. Provan, H. Grossman and R. Gray, *Wellesley Hospital, Toronto, Canada*

Between 1982 and 1986 intravenous digital subtraction angiography (IV DSA) was used to evaluate vascular grafts in 97 patients (54 men, 43 women). A total of 112 examinations were carried out for clinically suspected problems. Indications included recurrent symptoms, absent or diminished pulses or a drop in Doppler pressure measurements. In some patients it was difficult to be sure clinically whether the graft was patent or occluded. IV DSA was used to confirm the diagnosis.

IV DSA was performed by injecting 50 ml contrast (20–25 ml s^{-1}), through a 5 F pigtail catheter placed in the right atrium.

The rationale for chosing IV DSA was to look at the graft and anastomoses only. In 43 cases femoral popliteal grafts were evaluated, 23 were patent, 20 were occluded, 5 patients had stenosis distal to the insertion of the graft, there were 2 false aneurysms, 1 arteriovenous fistula and 1 popliteal embolus. In 42 aortobifemoral grafts evaluated, 23 were patent, 9 had a stenosis, there were 9 occlusions of one or both limbs of the graft, 4 false aneurysms, 11 patients had a stenosis in the vessels distal to the anastomosis and there was 1 kinked limb of a graft. Twenty-seven other grafts were evaluated: *in situ* femoropopliteal, axillofemoral, femorofemoral, aortorenal and aortosuperior mesenteric. Problems identified were: graft stenosis, stenosis of the anastomosis or in distal vessels, false aneurysm, arteriovenous fistula and emboli.

All findings were verified at surgery showing IV DSA to be 100 per cent accurate. Complications following IV DSA were that 2 patients developed hives and 1 thrombophlebitis. There were no cases of pulmonary oedema or death.

In conclusion IV DSA is very useful in the diagnosis of problem grafts if done on a selective basis to look at the graft and the anastomotic sites only. IV DSA is done on an outpatient basis, has good patient acceptance, is fast, safe and less expensive than conventional arteriography.

Duplex scanning in the follow-up of in situ vein distal bypass

P.J. Cullen, A.L. Leahy, D.J. Moore and D.G. Shanik, *Department of Vascular Surgery, St. James's Hospital, Dublin, Ireland*

Duplex scanning was used in the follow-up of 49 *in situ* infrapopliteal bypasses performed for limb salvage using the valve incision method. In 39 per cent the peroneal artery was the best available vessel for distal insertion; the anterior tibial and dorsalis pedis were used in 35 per cent and the posterior tibial artery and tibioperoneal trunk in 27 per cent. In the early postoperative period three fistulae presented with painful skin lesions. These were located using Duplex scanning and following ligation rapid resolution followed. Primary patency at one month was 87 per cent and was increased to 96 per cent by successful correction of four out of six failed bypasses.

A total of 11 stenoses were found in five bypasses 3–15 months postoperatively. In the majority of bypasses (four) the ankle/arm index decreased by at least 0·15 between reviews. A comparison was made between the spectral analysis on Duplex scanning and the findings on angiography and at operation. A peak frequency $>$ 6000 Hz was associated with 50 per cent or greater reduction in vein bypass diameter. The majority were corrected using vein patch angioplasty. Primary patency at 2 years was maintained at 68 per cent while correction of two out of seven bypass failures raised this to 80 per cent. Duplex scanning has allowed precise definition of vein bypass pathology. Correction is easily carried out and will be rewarded by an increase in long term limb salvage.

Relationship between plasma eicosanoids and cold sensitivity

D. Wilkinson, P. Vowden, A.B. Latif, S.M. Rajah and R.C. Kester. *St. James's University and Killingbeck Hospitals, Leeds, UK*

Abnormal prostaglandin metabolism may be an aetiological factor in cold sensitivity and may be reflected in abnormal plasma level of prostacyclin and thromboxane A2. We have measured the immunoreactive breakdown products of these eicosanoids (6-keto-PGF_{1a} and TXB_2) using a radioimmunoassay in healthy volunteers and in a group of patients with Raynaud's phenomenon (see *Table* below).

Patients with Raynaud's phenomenon secondary to a connective tissue disorder have markedly elevated 6-keto-PGF_{1a} and TXB_2 levels although the ratio of the two remains within our normal range. There is a significant difference between secondary Raynaud's phenomenon and all other groups investigated in the study (Mann–Whitney *U* test, $P = 0·04$). In primary Raynaud's phenomenon thromboxane levels and the TXB_2/keto-PGF_{1a} ratio tend to be elevated from our control values. Patients with vibration white finger disease have a similar eicosanoid profile to that of the primary Raynaud's group with elevated thromboxane levels. One patient in this group had markedly raised 6-keto-PGF_{1a} and TXB_2 levels and later proved to have a circulating auto-antibody. In the control group there was no significant correlation between eicosanoid levels and age, sex or smoking habits. Menstruating women in our study showed elevated thromboxane and TXB_2/6-keto-PGF_{1a} ratios similar to the primary group. It is interesting to note that menstruating women have an increased sensitivity to cold with abnormal cold stress tests.

Table

	Normals	Menstruating women
n	25	5
6-keto-PGF_{1a}	0·76 ± 0·52	0·86 ± 0·47
TXB_2	7·06 ± 5·06	12·06 ± 7·08
TXB_2/6-keto-PGF_{1a}	10·03 ± 3·01	14·00 ± 3·05

	Primary Raynaud's	Secondary Raynaud's	Vibration white finger disease
n	13	10	8
6-keto-PGF_{1a}	0·98 ± 1·04	31·01 ± 16·05	1·08 ± 2·00
TXB_2	15·00 ± 13·02	284·00 ± 9·00	27·01 ± 28·03
TXB_2/6-keto-PGF_{1a}	16·06 ± 3·06	10·04 ± 3·08	15·06 ± 4·07

All measurements expressed as mean ± s.d., ng/ml

Towards a living vascular prosthesis

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With a thought to improving long term patency of artificial (small diameter) arterial grafts, we have developed a sterile technique to culture adult human endothelial cells on vascular prosthesis.

Endothelial cells were harvested from human saphenous veins by collagenase digestion and cultured on cold insoluble globulin. Endothelial cell growth was confirmed by immunohistochemical staining and electron microscopy. In 23 cases, vein was obtained by a 'no touch technique' during varicose vein surgery: 87 per cent yielded a growth of endothelial cells which proceeded to confluence on 13 occasions (45 per cent). By contrast, only one vein of 15 (7 per cent) taken during coronary artery bypass surgery produced endothelial cell growth.

In a further 18 experiments, 1 cm square pieces of woven Dacron, and 30 x 5 mm (internal diameter) tubes of the same material were pretreated with cold insoluble globulin, and subcultured with previously passaged endothelial cells from varicose veins. On each occasion, endothelial cell growth was demonstrated.

Our techniques have shown that when adult human saphenous vein is isolated with meticulous care, it will provide an *in vitro* source of endothelial cells. Moreover, these cell lines can be subcultured onto Dacron grafts, to provide a prosthesis with a living layer of adult human endothelium.

Variability in the measurement of peripheral arterial disease

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The epidemiology of peripheral arterial disease is not well described compared to ischaemic heart disease and stroke. This is partly because of the need for simple repeatable techniques for measuring peripheral arterial disease in asymptomatic populations. The aim of this study, funded by the British Heart Foundation, is to determine the repeatability of two measurement techniques in order to assess their suitability for epidemiological research.

The study was conducted on 36 subjects aged 40–74 years (24 with peripheral arterial disease and 12 normal controls). Four specially trained observers conducted measurements under standard conditions on each subject in order to determine variability in ratios of ankle–arm systolic pressures and reductions in ankle systolic pressures after 4 min arterial occlusion (reactive hyperaemia test). The variability was determined between readings taken: successively on the same visit by the same observer; apart on the same visit by different observers; and on another visit 2 weeks later by different observers. The pressures in the arm and leg were assessed using a random zero sphygmomanometer with blood flow detected by means of a Doppler probe. In order to ensure balance with respect to any possible period and carry over effects by observers, a sequence was drawn up so that each observer took measurements on both first and second visits and on first and second groups of measurements within visits.

The results indicate not only the suitability of these measurement techniques for epidemiological research, but also the expected differences that may occur when measurements are repeated in clinical practice.

Reduction of narrow arterial graft thrombosis by defibrinogenation

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A new animal model has been developed to try to simulate the clinical problem of a narrow arterial graft into a poor run-off. A 3 mm internal diameter PTFE graft is inserted into a rabbit abdominal aorta and the distal run-off is reduced by narrowing both common iliac arteries using special clips, which reduce the graft flow by 50 per cent. This model was studied in 29 animals, 14 of which underwent defibrinogenation with Arvin. The drug was given in single subcutaneous daily doses of 20 units/kg body weight, starting 2 days before surgery and continuing for 2 days postoperatively. There was a significant difference in the perioperative plasma viscosity and whole blood viscosity at the low shear rate. The fibrinogen level was 2·8 ± 0·9 gl in the controls compared to 0·4 ± 0·3 gl in the treated group. The degree of defibrinogenation in these animals produced no problem with haemostasis during surgery or in the postoperative period. The cumulative patency rates in the controls at 24 h, 48 h and 4 days were 43, 28 and 28 per cent while in the Arvin group they were 86 ($P<0\cdot05$), 73 ($P<0\cdot05$) and 73 per cent ($P<0\cdot05$) respectively. All grafts patent at 4 days remained patent until the animals were killed 1–4 weeks later. Therefore in this model of a narrow PTFE graft with a poor run-off, defibrinogenation was a safe and effective method of improving the early patency. On the basis of this study, a multicentre clinical trial has been started in patients at high risk of early graft thrombosis.

Artificial circulation assessment of sapphire fibretips for use in laser angioplasty

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Safe and effective laser recanalization of occluded arteries relies on limiting damage to the normal or diseased vessel at the site of treatment. Perforation rates using bare fibretips are high; a way of reducing this is by modifying the fibretip. We have compared bare fibre angioplasty with the use of a hemispherically shaped sapphire fibretip in cadaver femoral arteries in an artificial circulation, using a Nd–YAG laser. Initial experiments showed that the energy threshold for clot formation was 20 J given over 4 s and the penetration rate of the fibretips through normal tissue under blood was 1 mm/s at 0·5 J/pulse. We examined 42 femoral arteries (25 occluded, 17 stenosed); only vessels which provided resistance to the passage of the 1·8 mm diameter probe were used. The laser fibre was introduced into the blood vessel via a standard 9 F angiography sheath. Circulation of whole human blood was started and laser energy was applied in increments of 5 J to a maximum of 1500 J, angiograms being taken after every 50 J. Recanalization of control vessels was attempted with the sapphire tip, but with the laser turned off.

Table 1 *Results*

Outcome	Controls ($n=14$)	Bare fibre ($n=14$)	Sapphire tip ($n=14$)
Successful recanalization	1	2	13
Failed recanalization	13	12	1
Perforation	0	9	0

Recanalization was mainly intraluminal; one of the vessels in the sapphire group showed some intramural dissection. The mean improvement in flow rate in the 10 occlusions recanalized with the sapphire tip was 0–54 ml/min and in the four stenoses was from 46 to 52 ml/min. The perforation rate was significantly greater with the bare fibretip than with the sapphire (Fisher's test, $P=0\cdot007$). Modified fibretips probably represent a significant advance towards safe human laser angioplasty; the procedure is more likely to be of benefit for occlusions than stenoses.

Lower limb oedema following femoropopliteal bypass grafting

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Successful revascularization of the lower limbs is frequently followed by distal oedema which may be troublesome and hinder rehabilitation. Venous thrombosis, damage to lymphatic channels and increased capillary hydrostatic pressure have all been implicated in the development of oedema[1]. Lymphoscintigraphy, a relatively non-invasive procedure, has recently been shown to distinguish clearly between limb oedema of venous or lymphatic origin[2].

We have studied 12 patients undergoing femoropopliteal bypass grafting. Pressures indices and foot volumes have been recorded in both lower limbs pre-operatively and 10 days postoperatively. Bilateral lower limb isotope lymphangiography has also been performed on the 10th postoperative day.

In the operated limbs, there was a significant increase in the postoperative pressure index (mean 0·56 ± 0·13 to 0·92 ± 0·16; Mann–Whitney U test, $P<0\cdot05$), associated with a significant increase in foot volume compared with the unoperated limb (relative increase >5 per cent; Mann–Whitney U test, $P<0\cdot05$). Lymphangiograms were performed of which 11 showed evidence of decreased lymphatic clearance and 1 showed increased transit time compatible with venous thrombosis, confirmed by venography. A further three patients have been investigated after transluminal angioplasty of femoral artery occlusions. Although pressure indices rose afterwards (0·60 ± 0·9 to

0·80 ± 0·03) there was no associated oedema at 10 days and lymphangiograms were normal, suggesting that increased hydrostatic pressure is not a cause of oedema when it occurs.

Isotope lymphangiography is less invasive than phlebography, and is useful in the investigation of troublesome post-reconstructive oedema which is usually due to peroperative damage to the limb lymphatics.

1. Vaughan BF, Slavotinek AH, Jepson RP. Oedema of the lower limb after vascular operations. *Surg Gynecol Obstet* 1970; **56**: 282–90.
2. Stewart G, Gaunt JI, Croft DN, Browse NL. Isotope lymphangiography: a new method of investigating the role of the lymphatics in chronic limb oedema. *Br J Surg* 1985; **72**: 906–9.

Single and multiple cerebrovascular events—correlation of ultrasound imaging and carotid plaque histology

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In this study of symptomatic carotid artery disease, the hypothesis is tested that multiple, embolic symptoms are associated with the discharge of athero-embolic material from a haemorrhagic cavity communicating with an atherosclerotic ulcer; and that single cerebral events result from the haemodynamic effect of closed haemorrhage into a non-communicating plaque.

Twenty-seven patients undergoing carotid endarterectomy (21 males, 6 females), with a mean age of 62 years, were studied by carotid ultrasound imaging angiography, cerebral CT scanning, and histological examination of endarterectomy specimens, including Pearl's stain to detect haemorrhage more than a week old.

Haemorrhage into a plaque was seen histologically in 21 patients (78 per cent), compared with 19 (70 per cent) diagnosed pre-operatively as heterogenous plaques on ultrasound imaging. The remainder were homogeneous, fibrous plaques. Only one case was diagnosed by contrast arteriography.

The excised endarterectomy specimens were inspected to determine whether the site of haemorrhage communicated with the base of an atherosclerotic ulcer. Communicating haemorrhages were present in 7 of 11 with episodic symptoms and non-communicating haemorrhages in 7 of 10 patients with a single cerebrovascular event. Pearl's stain showed recent haemorrhage in 7 of 11 patients with multiple symptoms, and old haemorrhage in 9 of 10 patients with a single event. There was no correlation with cerebral CT scans.

These findings suggest that ultrasonically heterogeneous communicating carotid plaques are symptomatically more active than homogeneous non-communicating plaques.

Early results of low dose intra-arterial streptokinase therapy in recent lower limb threatening arterial ischaemia

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In the last 12 months, 30 patients with critical ischaemia and 2 patients with severe claudication have received thrombolytic therapy using low dose intra-arterial streptokinase (5000 units/h) delivered by catheter directly to the site of the arterial occlusion. The mean age of the patients was 64 years (25–88 years) and there were 25 men and 7 women. The mean duration of ischaemia was 16 days and the most frequent cause was an arterial thrombosis (75 per cent). The most common sites were the femoral (53 per cent) and popliteal (34 per cent) arteries. The ischaemia was severe with loss of sensation or muscle paralysis in 12 (37·5 per cent) patients.

The mean duration of streptokinase perfusion was 38 h. Three patients failed to complete the infusion, one died from continued thrombosis and in two cases the arterial catheter caused a perforation of the popliteal artery, one case requiring urgent bypass surgery to achieve limb salvage. Other complications included minor groin haematomata (five cases), pericatheter thrombosis (six cases), accidental catheter removal (three cases) and distal embolization (two cases).

Lysis of the occlusion was initially achieved in 22 patients. The overall outcome at 30 days was: limb salvage, 22 (69 per cent); amputation, 8 (25 per cent) and death, 2 (6 per cent). The factor most influencing outcome was the severity of ischaemia, lysis being significantly more frequent in patients without severe ischaemia ($\chi^2 = 11{\cdot}1$, $P = 0{\cdot}001$). Thrombolytic therapy of recent arterial occlusions has proved safe and effective but its exact role requires further investigation.

Five year follow up of long-term aspirin/dipyridamole in femoropopliteal Dacron bypass grafts

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In a prospective, randomized, double blind study, the efficacy of aspirin (ASA) 330 mg t.d.s. and dipyridamole (DPM) 75 mg t.d.s. in maintaining Dacron femoropopliteal graft patency was compared with placebo. Seventy-three Microlevel prostheses were implanted in sixty-five patients for limb salvage and followed up for one year. Ten patients withdrew (nine active, one placebo). At 12 months, 4 out of 26 grafts had occluded in the active group (group 1) compared with 15 of 37 in the placebo group (group 2) (χ^2 with Yates' correction $= 5{\cdot}86$; d.f. $= 1$; $P < 0{\cdot}02$).

On the basis of these results and other studies, both groups were subsequently treated with ASA 300 mg daily and DPM 75 mg t.d.s. and were followed up for a minimum of 60 months (mean 72·5; range 60–86). Patency rates remained significantly higher in group 1 for up to 42 months ($P < 0{\cdot}05$ to $P < 0{\cdot}01$). Subsequently there was no significant difference and the 5-year patency for group 1 was 39 per cent compared with 35 per cent in group 2. Of 22 grafts patent at one year in group 1, 12 had occluded compared with 9 of 22 in group 2.

In group 2, 63 per cent of graft failures occurred in the first year, decreasing to 21, 8, 8 and 0 per cent in each subsequent year. In group 1, the timing was 25, 6, 19, 38 and 12 per cent.

These results demonstrate that ASA/DPM significantly increases graft patency over the first 24 months but suggest that long term use does not confer any benefit and may even be detrimental to graft survival.

Varicose veins surgery: effect of tourniquet on intra-operative blood loss and postoperative cosmesis

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An increasingly popular technique for the treatment of varicose veins is high tie of the saphenofemoral junction (SF) and avulsion of the varicosities below this level. Bleeding using this technique may be excessive and often obscures the remaining veins leading to inadequate surgery, bruising and a poor result.

We have recently compared the result of high tie and avulsions of varicose veins to that of high tie and avulsions after firstly exsanguinating the leg then using a pneumatic tourniquet at 500 mmHg. One hundred and twelve consecutive patients with SF, incompetence and blow outs beneath were randomized into the use of tourniquet or not. Volumes of blood and length of operation were recorded. Patients were seen at 3 weeks and 6 weeks using linear analogue scoring system by an independent observer and also were sent home with a linear scoring system to complete at 3 months.

Bruising and blood loss was significantly reduced using a tourniquet. Blood loss without a tourniquet ranged from 25 to 440 ml for each leg (median 121 ml). Using the torniquet, it was 2–56 ml, median 14 ml ($P = 0{\cdot}001$). The linear log score 0–10 assessed by patients at 3 months using tourniquet was 0·2 and without tourniquet was 0·7.

This technique had led to a marked reduction in blood loss and the number of swabs used, more elegant surgery and an improvement in cosmesis.

The morbidity of lower limb venous injuries in a civilian practice is significant

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Twenty patients were assessed clinically and by photoplethysmography (PPG), venous Doppler reflux and venography, following a venous injury in the lower limb. The median elapsed time was 17 months (range 0·5–66). The injuries had been sustained by gunshot (14) to the external iliac vein (1), common femoral vein (5), superficial femoral vein (6) and the popliteal vein (8) and 14 patients had an associated arterial injury. Five veins were ligated and the remainder repaired by end-to-end anastomosis (3), lateral repair (5), a venous patch (3) and interposition saphenous vein (4). The outcome was classified as good, fair or poor following clinical assessment (presence of oedema), PPG (recovery time

<17 s), the presence of popliteal venous reflux or venographic evidence of thrombosis.

Eleven patients had pedal oedema of the injured limb and two further patients had clinical evidence of a postphlebitic limb. The mean PPG recovery time ($\pm$s.d.) was $18{\cdot}9\pm11{\cdot}8$ s *versus* $32{\cdot}6\pm10{\cdot}7$ s ($P<0{\cdot}01$ Student's t test) in the injured and non-injured limbs respectively. Evidence of thrombosis was found in 7 of 12 venograms performed on limbs which had undergone previous repair. Ligation produced unacceptable morbidity and all end-to-end anastomosis initially failed. Two of four interposition saphenous venographs failed because of significant size mismatch and lateral repair resulted in stenosis in some patients. Overall 10 limbs (50 per cent) had a poor outcome. In this study lower limb venous injuries carried significant long term morbidity. Venous ligation should be avoided and the repair of choice is a vein patch or saphenous vein panel graph.

Bleeding through PTFE grafts

J.D. Baker, *Bristol Royal Infirmary, Bristol, UK*

There have been four cases in which there has been transudation of blood through PTFE grafts at the time of implantation. In each case the initial bleeding through needle holes stopped completely within 5 min with the application of topical thrombin. About 10 min after the graft had been opened there appeared a diffuse transudation of whole blood through the interstices of the graft (without further bleeding at the needle holes). Protamine administration and topical application of haemostatic agents failed to arrest the process. In each case the bleeding gradually subsided over a period of 30–60 min. The transudation of blood was unlike the chronic leakage of serum described in prior reports.

In reviewing each of these cases no abnormality or unusual feature could be found to explain the transudation encountered. Routine preoperative coagulation studies were normal. All grafts were handled according to the manufacturer's recommendations. Portions of two of the grafts were analysed with light and electron microscopy and were tested for porosity, but were in all ways similar to normal grafts.

The aetiology of this unusual complication has not been determined, but the process appears to be self-limited, stopping within an hour when it does occur.

How accurate is Doppler ultrasound in determining the level of the saphenopopliteal junction? Comparison with on-table venography

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The anatomical inconstancy of the saphenopopliteal junction is well known; failure to identify it at surgery may result in a high recurrence rate. The use of on-table venography for delineation of the anatomy has been well described[1] but it can be time consuming and technically difficult. This study was designed to assess the relative accuracies of Doppler ultrasound and peroperative venography in locating the saphenopopliteal junction.

With the patient standing the upper limit of reflux, audible with a unidirectional Doppler, was marked and compared with venographic and operative findings in 31 legs.

There was one false-positive detected by venography. Of the 30 true short saphenous vein problems Doppler assessment was correct to within 2 cm in 27 (90 per cent); the maximum error was 4 cm too low. Venography failed, for technical reasons, on three occasions and in two legs it was misleading. The Doppler mark proved useful in four of these cases and avoided multiple incisions.

Although on-table venography is superior to Doppler ultrasound for accurate localization of the saphenopopliteal junction the results of this study suggest that ultrasound is adequate for primary short saphenous vein surgery. Venography can be reserved for the difficult or recurrent cases.

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The results of excision of a cervical rib in patients with the thoracic outlet syndrome

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Neurological and vascular symptoms in the arms may be attributed to the thoracic outlet syndrome but there is doubt (elegantly expressed in an address to the Society by Dr Gilliatt) about the diagnosis. Similarly it is debatable whether one should resect a cervical rib if one is present in a patient with this syndrome. Cervical ribs are rare and evidence is anecdotal.

We describe the experience of one surgeon over 10 years of 21 resections of cervical ribs. Of these patients, 57 per cent had neurological symptoms, 43 per cent vascular and neurological symptoms and 24 per cent abnormal peripheral pulses. Cervical spondylosis and carpal tunnel syndrome were excluded after X-rays and electromyogram and all patients are seen by a neurologist.

At operation (supraclavicular) the subclavian artery was kinked in 24 per cent and there was one aneurysm. In all patients the rib impinged upon the brachial plexus.

Follow-up by interview and questionnaire showed 48 per cent completely cured, 52 per cent improved and only one patient experienced no benefit. Only 12 per cent of patients with vascular symptoms were cured compared with 67 per cent with neurological symptoms.

Surgical removal of cervical ribs is worthwhile in patients with the 'thoracic outlet syndrome'.

The place of first rib resection in the management of axillary–subclavian vein thrombosis

M.R. Pittam and S.G. Darke, *Royal Victoria Hospital, Bournemouth, UK*

Eight patients with axillary–subclavian vein thrombosis were studied. Three presented acutely and five presented with chronic symptoms of pain and swelling exacerbated by and limiting normal use.

Initial venography showed complete occlusion of the axillary vein in seven cases and marked narrowing in the remaining patient. Venographic evidence of narrowing or occlusion was also seen in 6/8 clinically normal contralateral arms. One of these arms became symptomatic 2 years later, and required surgery.

The patients presenting acutely were anticoagulated. Symptoms resolved slowly in two cases, but persisted in one. This patient and the five presenting with chronic symptoms, underwent decompression of the thoracic outlet, by transaxillary resection of the first rib.

Satisfactory decompression was confirmed at operation by eliciting and then abolishing 'nipping' of the surgeon's finger between the first rib and the clavicle on abducting and then relaxing the arm.

Symptomatic relief was achieved in 5/7 limbs thus treated (one patient had bilateral first rib resection). Although postoperative venographic improvement was seen in some cases, clinical success did not depend on recanalization of the main axillary–subclavian vein. The two patients with persistent symptoms after first rib resection subsequently had venous bypass procedures. Despite initial patency, both had occluded with return of symptoms within 4 months.

Survey of antibiotic use by members of the Vascular Society

G.T. Sunderland and A.J. McKay, *Western Infirmary, Glasgow, UK*

Our recent study of the intra-operative pharmacokinetic behaviour of two antibiotics (a cephalosporin and a penicillin) led us to be concerned at our use of prophylactic antibiotics in vascular surgery. We therefore conducted a postal survey of the 235 listed members of the Vascular Society of Great Britain and Northern Ireland. One hundred and eighty questionnaires (77 per cent) were returned and of these 177 (98·3 per cent) contained useful information. Of those responding, 68 per cent use prophylactic antibiotics in all vascular procedures. For aortic reconstruction 97·2 per cent used antibiotics, for infra-inguinal procedures 89·8 per cent use antibiotics. Cephalosporins (52 per cent) or a penicillin compound (44 per cent) were the most widely used agents. Prevention of graft infection was the principal reason given for use of antibiotics (96 per cent). There was considerable disparity in the length of time for which the antibiotic regime is used (median 1 day, range 1–7 days). There appears to be general awareness of the need for antibiotic prophylaxis in vascular procedures. However members of the Society are using preparations with specific antistaphylococcal activity to prevent graft infection. Such a narrow spectrum of activity may not be adequate[1]. Our own evidence suggests that as vascular surgeons we may have to use prophylactic antibiotics in a rather different regime to that followed in general surgical practice.

1. Bunt TJ. Synthetic vascular graft infections. *Surgery* 1983; **93**: 733–46.

Incidence of bowel colonization with Clostridium difficile in relation to duration of antibiotic chemoprophylaxis in aortic surgery

D.P. Nixon, R.T. Diggory, G.A. McLoughlin and C.A. Bartzokas, *Vascular Unit and Department of Medical Microbiology, Royal Liverpool Hospital, Liverpool, UK*

Antibiotic chemoprophylaxis is widely employed in vascular surgery to reduce the incidence and sequelae of graft and wound infection. The optimum postoperative duration of antibiotic administration is unknown with regard to prevention of infection whilst minimizing the side effects of the drugs.

A prospective study was undertaken to determine the incidence of antibiotic associated diarrhoea and pseudomembranous colitis (PMC) in patients undergoing elective aortic reconstruction. Two groups of 33 patients were randomized and given cephradine as antibiotic prophylaxis. Group 1 received the antibiotic with premedication and 6 hourly for 5 days postoperatively. Group 2 received the antibiotic with premedication and for 24 h postoperatively.

Stool samples were examined for *Clostridium difficile* culture (CDC) and *C. difficile* toxin (CDT) pre-operatively and with each stool passed postoperatively until discharge. Patients who developed diarrhoea and/or became CDC or CDT positive underwent sigmoidoscopy and biopsy.

No significant wound or graft infection occurred in either group. In Group 1, 6 patients developed diarrhoea and 9 were CDC and CDT positive, of whom 3 developed PMC. In Group 2, 3 patients developed diarrohea and none were CDC or CDT positive.

We conclude that the administration of cephradine for 5 days postoperatively in aortic reconstructive surgery is associated with an increased incidence of gut colonization with *C. difficile* and, in this study, actual development of PMC.

Ruptured aortic aneurysms: the coming storm

J. Collin, *John Radcliffe Hospital, Oxford, UK*

In spite of a greater readiness to perform elective abdominal aortic aneurysm surgery the number of patients with ruptured aneurysms referred for treatment appears to be relentlessly increasing. Is this increase real and will it continue?

The total number of recorded deaths from aortic aneurysm in England and Wales increased progressively from 3198 in 1964 to 7298 in 1984. It is unlikely that elective aneurysm surgery can have contributed more than 2 per cent of the extra 184 deaths. Age specific mortality rates for aortic aneurysm have shown a similar increase. In men aged 70–79 years mortality from aortic aneurysm increased from 0·69 per thousand in 1964 to 1·42 per thousand in 1984.

The incidence of ruptured abdominal aortic aneurysm is currently 6 times greater for men aged 75–79 years than 60–64 years and 12 times greater for women. In the 35 years to 1984 the total population between the ages of 75–84 years doubled. Population projections for the next 20 years point to an increase in the numbers over 75 years old of 20 per cent for men and 56 per cent for women.

The number of patients with a ruptured abdominal aortic aneurysm has increased substantially and will continue to do so for the foreseeable future with predictable consequences for vascular surgical workload and manpower.

Can we improve community mortality from ruptured aortic aneurysm

P.I.M. Allen, D. Tudway, M. Goldman, *East Birmingham Hospital, Birmingham UK*

Community mortality from ruptured aortic aneurysm exceeds 80 per cent, whereas elective aneurysm repair has a 5 per cent mortality, and remains a rewarding procedure even in the very elderly. To improve overall results there must be both efficient diagnosis of the aneurysm before rupture and prompt referral for surgery.

The potential benefit of screening for aneurysm was tested by inviting 146 elderly (>65 years old) hypertensives to undergo abdominal ultrasound examination. Seventy-five patients agreed to take part, nine aneurysms were found, but only one >5 cm merited surgery. The others will be reviewed.

We assessed the prospects for hospital referral by asking 74 general surgeons, 79 physicians, 74 geriatricians and 84 general practitioners how they would manage a fit 80-year-old woman with a palpable 6 cm infrarenal aneurysm; a situation with a 50 per cent risk of rupture within one year. Only 60 per cent of surgeons recommended surgery, and significantly fewer geriatricians (49 per cent), general practitioners (43 per cent), and physicians (37 per cent) thought surgery worthwhile ($P<0{\cdot}01$, χ^2).

The response to our clinical vignette showed that doctors in many specialities are unaware of the excellent results of elective aneurysm surgery. We suggest that until doctors understand that all clinically detectable aneurysms require early referral, screening alone is unlikely to affect overall mortality from ruptured aortic aneurysm.

Announcement

John Kinmonth Memoir

The idea of a Memoir of John's life and work was suggested at the Vascular Society meeting in November. Please send contributions for this in the form of letters, photographs or appreciations of his work to Kathleen Kinmonth Warren at 200 Highland Street, Dedham, Massachusetts 02026, USA by April 1987.

Correspondence

Fibronectin depletion after aortic surgery

Sir
We read with interest the report by Janet T. Powell *et al.* (*Br J Surg* 1986; 73: 38–40) concerning the appearance of fibronectin–hydroxyproline complexes in plasma after aortic surgery in patients and in a porcine experimental model. We noted, however, that the authors had used Haemaccel® (a gelatin-based colloid infusion) for resuscitation of the pigs. We showed in 1984[1] that after infusion of Haemaccel in humans, the ability of plasma fibronectin to bind gelatin was blocked for 24 h, most probably due to the formation of Haemaccel–fibronectin complexes. This effect was not seen, after dextran (Macrodex®). The gelatin (denatured collagen) that forms the Haemaccel macromolecules contains large amounts of hydroxyproline. We must thus express some doubts of the authors' conclusion that the presence of hydroxyproline in plasma in this setting was due to ischaemic insult.

The authors did not state which plasma expander they used during aortic surgery in patients; this information is necessary for the interpretation of their results.

F. Hesselvik
B. Brodin
H. von Schenck

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1. Brodin B, Hesselvik F, von Schenck H. Decrease of plasma fibronectin concentration following infusion of a gelatin-based plasma substitute in man. *Scand J Clin Lab Invest* 1984; **44**: 529–33.

Authors' reply

Sir
We are grateful to Dr Hesselvik and colleagues for reminding us of the untoward effects of Haemaccel® on plasma fibronectin levels. In their study (referenced above) fibronectin levels were depressed at 48 h and 72 h following Haemaccel infusion.

We described fibronectin depletion in 11 patients 6–24 h after aortic surgery. Only a single patient received Haemaccel intra-operatively or postoperatively. Therefore the fibronectin depletion must have resulted from factors other than Haemaccel.

Although our final protocol for the porcine model used Haemaccel for resuscitation it was not used in the first few animals where mortality and plasma hydroxyproline levels were highest. We had overlooked the hydroxyproline content of Haemaccel but are extremely puzzled why this was not reflected in high plasma hydroxyproline levels (~300 mg/l) in those pigs resuscitated with Haemaccel. We had determined that fibronectin was fully dissolved in thawed plasma samples but we should now investigate whether we are precipitating the degraded gelatin of Haemaccel during the separation or storage of plasma. The high molecular weight complexes we described are unlikely to have contained this degraded gelatin which has a molecular weight of only 30 000.

For these reasons we can reassure Dr Hesselvik and colleagues that the fibronectin depletion seen in our patients was not due to Haemaccel and we doubt that Haemaccel was the most important cause in our porcine model. More importantly still it is fibronectin depletion with concomitant loss of plasma opsonic function that has been associated with poor prognosis in intensive care unit patients. Hence, the main conclusion of our paper that fibronectin is depleted during major surgery and that the residual fibronectin may be in complexes, without further opsonic function, remains entirely valid. Clearly these concepts require further study.

Janet Powell
C. N. McCollum

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UK

Steel wire sutures and chemically induced rodent colonic tumours

Sir
We read with interest the article by Phillips and Cook (*Br J Surg* 1986; 73: 671–4) concerning the negative effects of persisting suture material on anastomotic site: steel wire sutures (as used in stapling instruments) were shown on this experiment to persist longer, to create more severe scarring reaction, and ultimately to favour anastomotic tumours. The role of this chronic inflammatory response generated by non-absorbable sutures as a promoter of carcinogenesis is suggested.

We conducted a similar study in order to compare long term healing of stapled and manual end-to-end anastomoses of the colon[1]: two anastomoses, one using the EEA 28 stapler, the other manual polyglycolic acid suture, have been constructed on the colon of eight mongrel dogs, after a simple intestinal section. Results were evaluated at 170±8 days. Macroscopic findings were similar in the two groups, except for the presence of staples in the digestive lumen for the stapled group. Radiography showed persistence of staples in each case. Histologically, stapled anastomoses showed persisting inflammation (*Figure 1*) despite the long follow-up. In contrast, manual suturing gave a firm scar with normal mucosa, and no or minor inflammatory changes.

Our experiments confirm in dogs the long-term inflammatory response observed in rats in the site of steel wire sutures. This may play a part in the late complications reported with this type of suturing[1,2].

P. A. Lehur
J. Visset

Hôpital G. et R. Laennec
Nantes
France

1. Malvy P, Visset J, Lehur PA, Gaillard F, Deret Ch., Paineau J, Potiron L. Désunion très tardive d'une anastomose colo-rectale mécanique. Rapport d'un cas et revue de la littérature. Approche expérimentale des complications tardives des agrafages circulaires. *Chirurgie* 1985; **111**: 650–8.
2. Lehur PA, Potiron L, Visset J. Correspondence. *Br J Surg* 1983; **70**: 508.

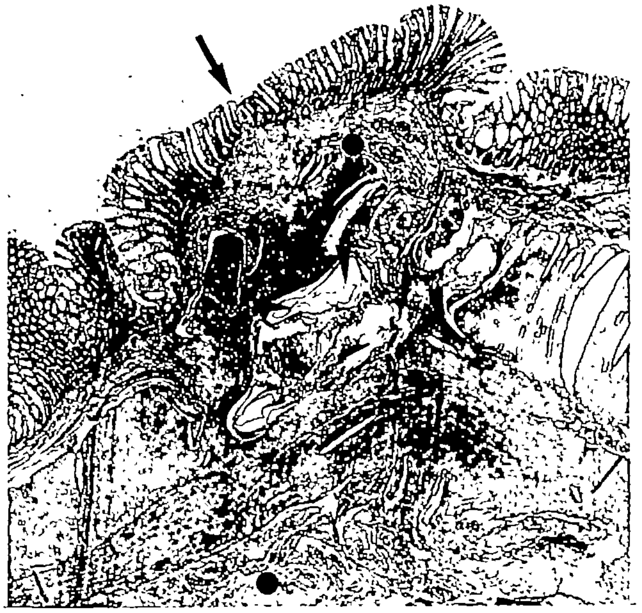

Figure 1 *EEA 28, Dog 2, 180 postoperative days. Haematoxylin and eosin × 3·5. Regenerative mucosa (→) above staple print in lamina muscularis propria (▶) and chronic inflammation in sub-mucosa and sub-serosa (●)*

Table 1 *Data represent cell numbers from W 163 tumour line adhering to 3 cm lengths of Prolene, stainless steel and Vicryl*

No. of times assay repeated	Prolene*	Stainless steel*	Vicryl*
3	1036 ±432	2505 ±1440	29 952 ±9690

Values are mean ± s.d.
* Manufacturer Ethicon

Sir

I read with interest the paper by R. K. S. Phillips and H. T. Cook (*Br J Surg* 1986; 73: 671–4) on the effect of steel wire sutures on the incidence of chemically induced rodent colonic tumours.

The model used in this study examines the effect of suture type on tumour induction at the site of a previously constructed anastomosis in dimethylhydrazine induced colon cancer. While this model has some analogy to human colon cancer, the appearance of a second primary in the region of the anastomosis is unlikely to be a significant cause of local tumour recurrence in humans. Perhaps more important in this setting is the presence of residual tumour cells following 'curative' resection of a primary colon cancer and the ability of certain sutures to adhere these tumour cells and initiate (by lowering the threshold cell number for tumour take) or potentiate local tumour recurrence.

In this respect, we have previously examined the adherence capacity of a number of different suture materials[1]. An examination of stainless steel as used in stapling devices demonstrated it to have a low adherence index for tumour cells (*Table 1*). In conjunction with this experimental evidence, a recent study by Wolmark and Associates[2], from the NSABP Prospective Clinical Trials examining local recurrence rates from stapled *versus* handsewn rectal anastomoses, demonstrated a 19 per cent local recurrence rate for the handsewn group compared with a 12 per cent local recurrence rate for the stapled group. These findings are in conflict with that presented by Phillips and Cook and do not support their suggestion, which is largely based on their own experimental model, that stainless steel wire should not be used when constructing an anastomosis after large bowel cancer surgery.

P. J. O'Dwyer

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1. O'Dwyer P, Ravikumar TS, Steele G Jr. Serum dependent variability in the adherence of tumour cells to surgical sutures. *Br J Surg* 1985; **72**: 466–9.
2. Wolmark N, Gordon PH, Fisher B *et al.* A comparison of stapled and handsewn anastomoses in patients undergoing resection for Dukes' B and C colorectal cancer. *Dis Colon Rectum* 1986; **29**: 344–50.

Hyperalimentation of jaundiced patients

Sir

I would like to comment on the article by Foschi *et al.* (*Br J Surg* 1986; 73: 716–19). These authors randomly allocated 64 patients with obstructive jaundice into receiving percutaneous transhepatic biliary drainage or biliary drainage plus hyperalimentation. The patients receiving hyperalimentation had lower morbidity and mortality than the patients having biliary drainage alone. The authors concluded that improving both hepatic function tests and the nutritional status of jaundiced patients can reduce the rate of complications after surgery for obstructive jaundice. Their data clearly do not support this conclusion. They defined malnutrition according to serum levels of albumin and transferrin, triceps skinfold thickness, the results of delayed hypersensitivity skin testing and a history of loss of > 10 per cent of pre-illness body weight. These indices would in themselves be sufficient to identify a group of patients at high risk of developing postoperative complications. However, the period of hyperalimentation did not alter any of these indices and it is, therefore, unacceptable to claim that 'improving... the nutritional status of jaundiced patients can reduce the rate of complications after biliary surgery'.

The second serious defect of this paper is their failure to give us information on the nutritional intake of the patients in the control group. These patients remained in the ward for a mean period of 15 days before surgical intervention, and presumably would have had free access to food and fluid during this time. It is possible that the patients were consuming adequate amounts of protein and calories despite not being allocated to the hyperalimentation group. I find it surprising that this information is not included in the paper. The authors mention that they measured urinary nitrogen excretion as an index of nutritional status of the patient. The significance of a positive urinary nitrogen balance is debatable, and to use it as an index of nutritional status is highly dubious. Since, however, the authors consider it to be important I would have expected them to have given us the results of at least cumulative nitrogen balance figures in both the fed and unfed group.

Undoubtedly, this study did show a difference between the two groups and I would suggest that a 'study group effect' is the explanation for this difference. Patients receiving hyperalimentation would have closer monitoring of their day to day fluid and electrolyte requirement and would certainly receive closer attention from nursing staff. I suspect this is the explanation for the improved outcome in the fed group. Alternatively, of course, it is possible that the differences arose by chance.

In the normal course of events those of us involved in nutritional research would be delighted to see the publication of a study which showed benefits from nutritional support. I am concerned by this study, however, since I believe it is scientifically flawed and its conclusions are misleading.

H. J. G. Burns

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Authors' reply

Sir

In his letter Dr Burns seems to reach to the conclusion that our patients who had hyperalimentation were malnourished after treatment, whereas patients who had no hyperalimentation were probably well-nourished. He thinks that the different mortality and morbidity rates between the two groups of treatment could be explained by causes other than an improvement in the nutritional status after hyperalimentation, for instance, more accurate care by the nursing staff of the patients in hyperalimentation or chance ($P < 0{\cdot}01$).

In our opinion his conclusions can be explained as follows.

(1) Dr Burns identifies the markers of malnutrition as malnutrition. Although it is difficult to define malnutrition, there is no doubt it is a metabolic condition which includes changes in body composition[1]. When hyperalimentation is given for 14 days, the metabolic processes of malnourished patients are restored, but body composition still remains abnormal[2]. We stressed in the discussion section that nutritional markers cannot be used to monitor hyperalimentation. However the prognosis for surgical patients on pre-operative hyperalimentation for 7 days was greatly improved, as a specific effect of the improvement of the nutritional status[3].

(2) Dr Burns complains that the nutritional intake of patients in the control group was not given. He is right and we apologise. However, it is known that jaundiced patients who have no bile or pancreatic enzymes cannot digest and absorb lipids and proteins. As stated in the discussion section, this is one of the main causes of malnutrition in jaundiced patients and it remains in effect during external drainage of the biliary tract. Since the daily diet will not be absorbed by the patients, it is unlikely that any diet except the elemental diets would have greatly improved the nutritional status of the patients.

(3) We feel that the absence of details of the urea nitrogen balance is a minor issue. We used it as an indication of sufficient N intake and establishment of a correct N/caloric ratio.

The final comment of Dr Burns is based on his personal feeling about the subject and on criticisms that we feel are not valid.

Finally, we were happy to see our conclusions confirmed in a recent article of Dr Jeppsson[4], who reported hyperalimentation to be effective for jaundiced patients on PTBD when sepsis is avoided.

Reproducibility of the positive results by other groups is the best answer to any criticism.

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1. Kinney JM. Protein-energy malnutrition in surgical patients. In: Hill GL, ed. *Nutrition and the Surgical Patient.* Edinburgh: Churchill Livingstone, 1981: 13.
2. Bennegard K, Eden E, Ekman L, Schersten T, Lundholm K. Metabolic response of the whole body and peripheral tissues to enteral nutrition in weight-losing cancer and noncancer patients. *Gastroenterology* 1983; **85**: 92–9.
3. Mullen JL, Buzby GP, Matthews DC, Smale BF, Rosato EF. Reduction of operative morbidity and mortality by combined preoperative and postoperative nutritional support. *Ann Surg* 1980; **192**: 604–13.
4. Jeppsson B, Halliday AW, Blumgart LH, Bengmark S. Pre- and postoperative nutrition in liver surgery. In: Bengmark S, Blumgart L, eds. *Liver Surgery.* Edinburgh: Churchill Livingstone, 1986: 166.

Nerve tumours of the brachial plexus

Sir

The recent paper of Sell and Semple (*Br J Surg* 1987; **74**: 73–4) fulfils an important task in reminding surgeons of the problems of tumours recognized to be arising from nerves. Correctly they point out that neurilemomas are not thought to undergo malignant transformation. However, some reference does need to be made to malignant tumours of recognizable nerves with which neurilemoma and neurofibroma may be confused. When, in the absence of von Recklinghausen's disease, a solitary tumour is found at operation to be arising from nerve, then it is most probably a neurilemoma, and if so can usually be shelled out of the nerve provided the right plane is entered. When there is no ready plane of cleavage, but on the contrary where the nerve is diffusely involved, then the tumour may be malignant, or it may be a diffuse neurofibroma[1].

A grossly plexiform involvement of deep nerve is usually associated with von Recklinghausen's neurofibromatosis. In the absence of clinical or operative findings suspicious of malignancy it is often best left alone. Removal would usually be incomplete and produce palsy; it would not free the patient of the risk of further plexiform change or malignant degeneration of the proximal nerve or nerve roots. On the other hand, if left it may remain stationary for years, though it does carry some risk of malignancy.

In the presence of neurofibromatosis a discrete tumour of deep nerve may occasionally be a neurilemoma but is more commonly a neurofibroma and quite likely to be a sarcoma. Before radical treatment can be undertaken histological evidence must be at hand. There may be clinical evidence favouring the possibility of malignancy: recent pain or increasing size, referred pain (though this is almost equally common in the benign tumour of recognizable nerve) and especially motor weakness or impaired sensation (which is rarely seen in benign tumours unless confined as by bone). Where the features are strongly suggestive of sarcoma it is wise to perform a superficial biopsy, disturbing the tumour as little as possible. Radical treatment follows confirmation of diagnosis. When the biopsy is inconclusive, and in those cases in whom in the first instance there is no especial evidence of malignancy, the tumour is exposed and its relationship to the nerve defined. The malignant tumour tends to infiltrate along the nerve and later to penetrate the sheaths and extend into the surroundings. Biopsy of discrete neurofibroma of the deep nerves is unreliable since only one part of the tumour may have undergone malignant change.

The great value of a preliminary segmental biopsy lies in identifying those cases of encapsulated neurilemoma which are not typical in their gross appearance and in whom a conservative approach would be justified when affecting an important nerve.

In frank sarcoma of deep nerves the prognosis is extremely grave. (The less common superficial sarcomas appear to be less malignant.) However it is much more likely that a tumour of a deep nerve will be a neurilemoma, a benign tumour, and it is desirable that surgeons who will only encounter the problem very occasionally should be aware of this and avoid the tragedy of producing major nerve damage needlessly.

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1. Heard G. Nerve sheath tumours and von Recklinghausen's disease of the nervous system. *Ann R Coll Surg Engl* 1963; **31**: 229–48.

Book reviews

Secondary Prevention of Colorectal Cancer: Frontiers of Gastrointestinal Research No. 10

P. Rozen and S. J. Winawer. 245 x 175 mm. 273 + xiii. Illustrated. 1986. Switzerland: S. Karger AG, Basle. £77.70.

We must stop large bowel cancer. As yet we do not seem to know enough to prevent the malignant process starting, so we are left with secondary methods designed to nip it in the bud at the premalignant or early invasive stage. Rozen and Winawer and a number of internationally distinguished contributors here guide us through epidemiology, general principles, and techniques for screening average and high risk populations to a number of progress reports from screening programmes around the world.

I liked the book: the wealth of references (199) in the first chapter on epidemiology; the wonderfully complex areas of law and ethics (what is violation of the right of privacy and how often is well intentioned genetic enquiry seen as offensive by some blissfully ignorant next of kin?); the success and failure stories of cancer screening clinics and community programmes; the disagreements—immunological tests for human blood in stool using antibodies have reduced sensitivity, require complete and homogeneous stool preparation, require too long for the assay to be done and will probably demonstrate little advantage over the less costly and easier to perform guaiac procedures (Fleisher and Schwartz from the Memorial Sloan–Kettering Cancer Center in New York), as against 'the detection of faecal occult blood using immunological tests has many advantages as the test is specific for human haemoglobin and the sensitivity of the test can be adjusted' (Lee and Hardcastle from Blackpool and Nottingham respectively); and the discovery—to become acculturated (*sic*).

The progress reports were dull in parts, and the book is expensive (£77.70).

R. K. S. Phillips

Pathways in Surgical Management. Second edition

M. Hobsley. 245 x 190 mm. Pp. 362. Illustrated. 1986. London: Edward Arnold. £23.50.

This is a book of algorithms and, as Professor Hobsley states in the preface to his first edition, it is related to a textbook of surgery in the same way that a thesaurus is related to a dictionary. Conventional surgical textbooks tend to discuss diagnoses. This book discusses problems as they would appear to the practising surgeon and proceeds to establish for each not a differential diagnosis, but a working diagnosis on which subsequent decisions of management are made. We all tend to do this, even if subconsciously. For example, there may be a large differential diagnosis for a lump in the breast but for most patients the working diagnosis is carcinoma until proved otherwise. Each of the problems is looked at in this light.

Professor Hobsley had chosen 19 non-emergency topics and 10 emergencies, covering a very wide spectrum of surgery, and for each topic flow diagrams of management are established. Appropriate and due emphasis is placed upon the conventional skills, that is to say the taking of a good history, careful examination for physical signs and the undertaking of appropriate investigations, starting with the most simple and progressing to the more complex as the pattern of the patient's illness unfolds. It remains true that many patients seen in surgical outpatients have nothing more than a history to offer, since examination may reveal no physical signs.

I have to confess to not particularly liking algorithms, and some of the flow diagrams in this book are incredibly complex. These, I think, in some ways may confuse rather than clarify the situation. The plans of actions outlined are sometimes more suitable for use by a binary computer and the high quality text is sometimes made difficult to follow by the serial insertion of repeat algorithms. There is a good bibliography, references being selected by virtue both of their quality on the topic under discussion and also providing a good selection of references for further reading. The index appears to be well constructed and, despite my minor reservations about flow diagrams, I would regard this second edition as an extremely valuable addition to the library of students and established surgeons alike. For the latter Professor Hobsley has written a very cerebral book. There is a great deal of food for thought in the various topics which he discusses. I would thoroughly recommend it, not just for libraries but for personal use as well.

M. H. Jourdan

A Colour Atlas of Vascular Surgery

J. S. P. Lumley. 310 x 255 mm. Pp. 350. Illustrated. 1986. London: Wolfe Medical Publications. £75.00.

When I was asked to review the Atlas of Vascular Surgery I undertook it with less than an open mind because I am an admirer of the author who is a surgeon of considerable stature. I had also just read a textbook of vascular techniques by an Anglo-French partnership which is produced with black and white line drawings and is wholly admirable.

The Atlas of Vascular Surgery contains step by step descriptions of all the routine operations and some which are not routine, illustrated by numerous plates in full colour. Details in the pictures are not arrowed and unless the reader is familiar with the subject they can be confusing. This and the absence of indications for operation and complications detract from its usefulness to surgeons in training. In this respect the book suffers in comparison with its Anglo-French counterpart. This is not meant to detract from the technical brilliance of the photographs, only to underly the fact that one needs to know the steps of the operation in order to interpret the pictures. In elegant homes, the interiors of which are familiar to us through the pages of glossy magazines, occasional tables are furnished with lavishly illustrated catalogues of the works of Bruegal, Rembrandt and Reynolds; this atlas would admirably serve a similar purpose in the salons of Harley Street.

D. Charlesworth

Hernia Repair Without Disability. Second Edition

I. L. Lichtenstein. 285 x 220 mm. Pp. 252+xii. Illustrated. 1986. Missouri, USA: Ishiyaku EuroAmerica, Inc. $85.00.

Irving L. Lichtenstein has been 'exploding the myths of hernia repair' since 1976. This beautifully produced book, described on the title page as 'a surgical atlas . . . of the one day hernia', is another salvo in his war on myth.

Lichtenstein undoubtedly has good ammunition but his battleground control is weak, his strategic objectives are unclear and his intelligence gathering, so essential to a successful campaign, inadequate and at times frankly incorrect. A disheartening example of his poor intelligence gathering and grasp of the literature is his condemnation of the work of the late W. J. Lytle of Sheffield. He incorrectly accuses Lytle of suturing the deep inguinal ring lateral to the cord in inguinal herniorrhaphy. After reading this allegation I went over and checked all the Lytle references in the library, including those quoted in this book. Lytle did recommend repair of the deep ring, he repaired it medial to the cord and in doing so endeavoured to preserve the shutter action of the deep ring pillars to make his repair physiologically sound. It was an earlier American, rich in rhetoric and short of fact too, who recommended lateral repair of the deep ring. The culprit, A. H. Fergusson, described his operation in 1899. The literature review in this book leaves much to be desired: not only is it incomplete and inexact but the sources are not indexed against the text, making checking of the references impossible.

Vague, unreferenced statements abound, for example 'the differential diagnosis of direct, indirect, inguinal and femoral hernias . . . can be made with a reasonable degree of accuracy'. What is 'reasonable'? and is there any research data to support this contention? None is cited. Contradiction appears on the next page, 'an encysted hydrocele will mimic hernia exactly. Differentiation is established at surgery'. Lichtenstein rails against authors who published inadequate follow-up data, then details all his results in '6321 consecutive herniorrhaphies' as percentages of the total. I found this one table meaningless; there are no time-related follow-up data, just a statement of a recurrence rate of 0·7 per cent with 91 per cent of patients (all types of hernias) followed up from 2 to 14 years. Compared with the careful statistical methods used by other North American herniologists these data give nothing away.

The book is not a complete atlas of hernia surgery, many hernias and operations are not included. Children's hernias, obturator and other pelvic hernias and peristomal hernias are not included. Important techniques, pneumoperitoneum and extraperitoneal mesh for instance, are not described. The index is very poor too.

In summary this book does not cause much of an explosion among the myths of herniology, it is really a well produced damp squib and not recommended by your reviewer.

H. B. Devlin

Anatomical Studies for Renal and Intrarenal Surgery

F. T. Graves. 250 × 190 mm. Pp. 213 + xv. Illustrated. 1986. Bristol: John Wright & Sons Ltd. £49.50.

Mr Graves' work and publications on the anatomy and nomenclature of the renal circulation are well known to urologists in particular. The technique which he has evolved for demonstrating the arterial tree is highly effective, and results in some stunning photographs. The renal surgeon will be grateful to Mr Graves for describing in detail the arterial inflow of the horseshoe kidney, before having to tackle an infrequent pyeloplasty or (dare I say it) open nephrolithotomy of that organ.

With the advent of percutaneous renal surgery, the younger surgeon may be less familiar than his elders with the eccentricities and abnormalities of the vascularity of the kidney; and yet may find that partial nephrectomies for hypernephroma and other unthinkable operations are necessary. Once again, he will be grateful to Mr Graves' detailed work.

That part of this book concerned with calculus disease is of interest but somewhat bitty. The aetiology of this disorder will almost certainly be due to the derangement of a physiological process rather than an anatomical abnormality. The resin casts of the convoluted tubules are quite beautiful, but I would hesitate to develop a hypothesis related to stone formation on the basis of acute angled bends of some of these tubules. Similarly, I am somewhat unhappy about the interpretations accorded to the fascia which envelopes the renal pelvis and upper ureter, which he suggests may be a cause of pelviureteric junction.

The forte of this book lies in the first dozen chapters (this accounts for half of the book) and it is unreservedly recommended as a most comprehensive text on the vascularity of the kidney.

C. A. C. Charlton

Treatment and Prognosis. Surgery

R. L. Hawkins. 230 × 155 mm. Pp. 278 + xix. 1986. London: William Heinemann Medical. £9.95.

This is one of a series of books entitled *Treatment and Prognosis* which aims to concentrate on the essential core of information common to the practice of general practitioners and hospital doctors. This volume concerns surgery alone and the medical volume was published simultaneously. Further *Treatment and Prognosis* texts are anticipated in Paediatrics and Obstetrics, and Gynaecology. The series editor is Richard Hawkins, formerly of the *British Journal of Hospital Medicine* and *World Medicine*. Each topic selected begins with a short précis including pathology and epidemiology and is followed by a section on prognosis and then one on treatment. Some guidance is offered about follow-up. It is interesting and instructive to test your own opinions, memories and prejudices against the text which is supported by a few strategic references. Surgery is divided into thirteen topics and twelve are covered by single authors. This volume covers much ground and is informative and stimulating. It will help update the knowledge of all who use it.

The series is entitled *Treatment and Prognosis* but the order throughout the thirteen chapters is always prognosis first and treatment second. Perhaps the instructions to authors could be changed for the updated editions which will be published from time to time. Some topics appear in two chapters and one could be eliminated with benefit.

This is an enjoyable book to use and is excellent value at £9.95. Use it and the reader will benefit.

J. B. Bourke

Pathology for the Primary FRCS

D. L. Gardner and D. E. F. Tweedle. 225 × 150 mm. Pp. 216. Illustrated. 1986. London: Edward Arnold. £11.95.

This concise book aims to provide candidates with the correct answers to questions likely to be asked during the oral part of the examination in pathology for the primary FRCS. Both authors are examiners in pathology at the Royal College of Surgeons of Edinburgh and therefore know the requirements necessary to pass the examination in Edinburgh. Although they comment that there is no published syllabus for this examination, the Royal College of Surgeons of England does have one and requires candidates to understand the basic principles underlying disease processes and lists the topics with which they should be familiar. It is a fact, however, that questions now asked in all four Colleges far exceed the basic principles and all candidates are expected to have a much wider knowledge of pathology. Attainment of this high standard is one of the virtues of the primary examination in its present day form, as failure to pass helps to eliminate those candidates not destined for a surgical career. To some extent the contents of this volume cover all the subjects and come close to providing a syllabus for the examination. The topics are set out in alphabetical order but none is discussed in detail. Basic terms such as hyperplasia and hypertrophy are merely defined and exmaples are not quoted, leaving the reader to refer to other text books.

As stated in the foreword, it is not a book to read straight through from cover to cover, but it is a handbook which serves a somewhat useful purpose in preparation for the oral examination of the primary FRCS. In those Colleges where there is a compulsory written essay paper, further reading is mandatory and probably also necessary for the multiple choice questions section.

N. V. Addison

Chirurgie '86. Association Française de Chirurgie

M. Malafosse. 240 × 160 mm. Pp. 181 + x. No illustrations. 1986. Paris: Masson. 125 fr.

This book, in French, is a collection of the summaries and the outline of proposed forum discussions of the 88th French Congress of Surgery in September 1986 in Paris. This book was published nearly 6 months before the Congress so that the participants could have prior knowledge of the papers to be presented and the anticipated discussions. It was not received for review until after the Congress.

A variety of subjects are treated including cancer, trauma, abdominal surgery and also some vascular, gynaecological and orthopaedic surgery. In a book of this kind only a few of the summaries include references. There is no index but the contents pages are helpful and list each paper with its author.

This publication is primarily intended for those who participated in the Congress and as such will surely have been very helpful. It is only of limited value to the non-participant who may, however, find it helpful if he is interested to know the subject discussed at the last French Congress of Surgery and the names of the various speakers.

G. H. Jantet

British Medical Bulletin. Endoscopic Surgery. Vol. 42, No. 3, July 1986

R. A. Miller and J. E. A. Wickham. 275 × 215 mm. Pp. 221–339. Illustrated. 1986. Edinburgh: Churchill Livingstone. £16.00.

Endoscopy has had a profound influence on many branches of surgery over the last 15 years. Prostatectomy is performed endoscopically in over 90 per cent of patients in many centres. Gastroscopes and colonoscopes are used every day by gastrointestinal surgeons, and gynaecologists use laparoscopes routinely for procedures as diverse as retrieving ova for *in vitro* fertilization and sterilization. This bulletin brings together a review of endoscopic surgery from many disciplines, not only to report the present state of the art, but to look into the future. It is worth reading just for the provocative introduction in which Mr Wickham prophesies that within the next 30 years most cold abdominal surgery will be done by 'interventional radiologists and minimally invasive surgeons. The only remaining areas for open surgery would be those of trauma and reconstructon.' Although this probably overstates the case, surgical training must take account of the rapid changes in surgical techniques.

The rest of the volume gives accounts of the history and development of endoscopy and its wide application. Both rigid and flexible endoscopes are described with just enough technical detail for the practising surgeon. The newest techniques of fetoscopy and vascular endoscopy are described and in the latter chapter a timely warning is given that widespread clinical application of coronary angioscopy requires a definite indication and advantage over existing diagnostic methods. The latter part of the bulletin covers tissue destruction techniques such as laser endoscopy and advances in endoscopic diathermy. The volume ends with a brief look at veterinary endoscopy—the horse having endoscopy of his pharynx and larynx seems more relaxed than many patients! There are line drawings, photographs and references after each section. It is a comprehensive and forward looking review.

A. G. Johnson

Notices and announcements

Meetings

27–28 April 1987
International Symposium on Reoperative Infrarenal Arterial Surgery
Rigshospitalet, State University Hospital, Copenhagen, Denmark
Information: International Symposium on Reoperative Infrarenal Arterial Surgery, Department of Surgery D, Section of Vascular Surgery, Rigshospitalet, State University Hospital, 9 Blegdamsvej, DK-2100 Copenhagen Ø, Denmark

28–30 April 1987
Annual Meeting of The American Laryngological, Rhinological and Otological Society
Denver, Colorado, USA
Information: Dr Roger Boles, President, c/o Lilibet Coe, Administrative Assistant, Kutztown Road, East Greenville, PA 18041, USA

9–15 May 1987
Digestive Disease Week of the American Gastroenterological Association
Chicago, Illinois, USA
Information: Registration Supervisor, Slack Inc., 8900 Grove Road, Thorofare, NJ 08086, USA

10–13 May 1987
Joint Annual Meeting of the American Lung Association, the American Thoracic Society and the Congress of Lung Association Staff
New Orleans, Louisiana, USA
Information: American Thoracic Society, 1740 Broadway, New York, NY 10019, USA

10–13 May 1987
XXII Congress of the European Society for Surgical Research
Aarhus, Denmark
Information: Aarhus Turistforenings Kongresbureau (Convention Bureau), Radhuset, DK-8000 Aarhus C, Denmark

15–16 May 1987
Fifth International Nijmegen Vascular Symposium 'Angioplasty—Vascular Surgery—Combined Approach'
Nijmegen, The Netherlands
Information: Dr S. H. Skotnicki, St. Radboud Hospital, PO Box 9101, 6500 HB Nijmegen, The Netherlands

20–23 May 1987
78th Annual Meeting of the American Association for Cancer Research
Atlanta, Georgia, USA
Information Margaret Foti, American Association for Cancer Research Inc., Temple University School of Medicine, West Building, Room 301, Broad and Tioga Streets, Philadelphia, PA 19140, USA

22 May 1987
British Association of Endocrine Surgeons
Edinburgh, UK
Information: Mr A. W. Goode, Honorary Secretary to the British Association of Endocrine Surgeons, Surgical Unit, The London Hospital, Whitechapel, London E1 1BB, UK

24–30 May 1987
Annual General and Scientific Meeting of the Oto-laryngological Society of Australia
Surfers Paradise, Queensland, Australia
Information: OLSA Meeting Secretariat, PO Box 731, Toowong Q4066, Australia

1–3 June 1987
International Congress of Abdominal Infections
Hamburg, FRG
Information: D. H. Wittmann, Priv. Doz. Dr. I. Chir. AK Altona, Paul-Erlich-Strasse 1 D-2000, Hamburg 50, FRG

6–7 June 1987
Course on the Applied Surgical Anatomy and Operative Surgey of the Liver, American Association of Clinical Anatomists
Toronto, Canada
Information: Dr R. Ger, Winthrop University Hospital, Mineola, NY 11501, USA

10–12 June 1987
69th Meeting of the Endocrine Society
Indianapolis, Indiana, USA
Information: The Endocrine Society, Annual Meeting Office, 428 E Preston Street, Baltimore, MD 21202, USA

15–19 June 1987
Advanced Hepato-Pancreatico-Biliary Surgery
Lund, Sweden
Information: Professor S. Bengmark, Box 5121, S-220 05 Lund 5, Sweden

22–26 June 1987
Peritoneum and Peritoneal Access
Lund, Sweden
Information: Professor S. Bengmark, Professor of Surgery, Box 5121, S-220 05 Lund 5, Sweden

24–28 June 1987
Annual Meeting of the Western Thoracic Surgical Association
Colorado Springs, USA
Information: Western Thoracic Surgical Association, 13 Elm Street, Manchester, MA 01944, USA

7–8 July 1987
Blood Flow '87 (Biological Engineering Society - Blood Flow Group)
University of Leeds, UK
Information: Mr R. Price, Department of Medical Physics, Leeds General Infirmary, Leeds LS1 3EX, UK

9–10 July 1987
Surgical Research Society Meeting
Leeds, UK
Information: Professor I. Taylor, Surgical Research Society, University Surgical Unit, F Level, Centre Block, Southampton General Hospital, Tremona Road, Southampton, UK

9–11 July 1987
XIIth International Update on Liver Disease
London, UK
Information: Professor Neil McIntyre, Academic Department of Medicine, Royal Free Hospital, Pond Street, London NW3 2QG, UK

11–12 July 1987
Summer 1987 Hong Kong Surgical Forum
Hong Kong
Information: Forum Secretary, c/o Department of Surgery, University of Hong Kong, Queen Mary Hospital, Hong Kong

31 August–4 September 1987
Surgical Efficiency and Economy
Lund, Sweden
Information: Professor S. Bengmark-SEE, Box 5121, S-220 05 Lund 5, Sweden

9–11 September 1987
Clinical Controversies in Inflammatory Bowel Diseases
Bologna, Italy
Information: Organizing Secretariat, SO.GE.PA.CO. Spa. piazza Constituzione, 5/c, 40128, Bologna, Italy

15–18 September 1987
The British Society of Gastroenterology Jubilee Meeting
London, UK
Information: The Administrative Secretary, The British Society of Gastroenterology, 3 St Andrew's Place, Regent's Park, London NW1 4LB, UK

11–16 October 1987
Annual Clinical Congress of the American College of Surgeons
San Francisco, California, USA
Information: American College of Surgeons, 55 East Erie Street, Chicago, Illinois 60611-2797, USA

18–24 October 1987
Recent Advances in Pancreaticobiliary Surgery
Glasgow, UK
Information: Professor D. C. Carter, University Department of Surgery, Queen Elizabeth Building, Royal Infirmary, Glasgow G31 2ER, UK